S. HRG. 106–447

GENE THERAPY: IS THERE OVERSIGHT FOR PATIENT SAFETY?

HEARING

BEFORE THE

SUBCOMMITTEE ON PUBLIC HEALTH

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS UNITED STATES SENATE

ONE HUNDRED SIXTH CONGRESS

SECOND SESSION

ON

EXAMINING CERTAIN ISSUES REGARDING PATIENT SAFETY IN GENE THERAPY CLINICAL TRIALS, FOCUSING ON FEDERAL OVERSIGHT PROCEDURES AND GUIDELINES FOR INFORMING PATIENTS AND THEIR FAMILIES OF POTENTIAL RISKS AND BENEFITS OF GENE THERAPY

FEBRUARY 2, 2000

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WEDNESDAY, FEBRUARY 2, 2000

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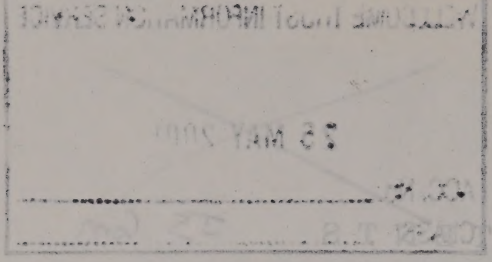

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U.S. SENATE,
SUBCOMMITTEE ON PUBLIC HEALTH, OF THE COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The subcommittee met, pursuant to notice, at 9:35 a.m., in room SD–430, Dirksen Senate Office Building, Senator Frist (chairman of the subcommittee) presiding.

Present: Senators Frist, Jeffords, Hutchinson, Kennedy, Bingaman, and Dodd.

OPENING STATEMENT OF SENATOR FRIST

Senator FRIST. Good morning and welcome, everyone, to today's hearing on what are truly critical issues regarding the subject of patient safety in gene therapy clinical trials.

The events of the past few months involving gene therapy research have given all of us, our Government and our society, reason to pause and have prompted the subcommittee today to undertake and initiate a thorough review of this truly revolutionary research field and the systems that surround it.

Today's hearing is a very important one. We will be talking about death, we will talking about life. We will be talking about promising new research that could not have even possibly been imagined 30 years ago. We will be talking about the tough ethical issues such as informed consent and what conflict of interests exist with the research community. We will be talking about the nature of experimentation in human beings—inherently risky, fundamentally profound. We will be talking about gene therapy, what is gene therapy, how does it differ from other therapy, and what promise does it hold for each of us and for our children.

Gene therapy is an experimental procedure whose effectiveness has not yet been demonstrated, but it does offer real hope and real promise for those people who are suffering from genetic and nongenetic diseases. It holds great promise, but because it is experimental, there is an absolute necessity that we in Government and in the private sector provide appropriate and vigilant oversight.

If we ask patients to participate in clinical trials to more promising science forward, we must assure them that their safety is first and foremost.

I hope that today's hearing will be a thoughtful discussion and will provide a thorough review of the oversight mechanisms that

are in place, both in place on paper as well as giving us the opportunity to see whether what is on paper is actually being carried out.

Doctors and scientists do have what I regard as a truly noble journey to pass along promising research and to explore that research in an appropriate way in this new scientific field. But in that journey, there is absolutely no place for mistakes that compromise patient safety.

The tragic death of Jesse Gelsinger, who was the first patient we learned about who died from gene therapy, has sombered us all. Jesse, as all of you know, was 18 years old. He had a rare liver disease. He unselfishly volunteered for a gene therapy clinical trial which was designed not to cure him but to develop a treatment that others, children and babies, could benefit from in the future.

Mr. Paul Gelsinger, Jesse's father, has generously agreed to be with us here today, and we offer our deepest condolences to the Gelsinger family and our true gratitude that he comes before us at a painful time in his own life to share with us his experience and to help us learn how we can make the big picture better and make the system better. As we will hear Mr. Gelsinger graphically describe today, we absolutely must chart a new path that ensures that no family will have to endure what he and his family have had to endure over the last several months.

Yet I predict that in the future, we are going to continue to learn more about adverse events that have occurred in gene therapy trials. Just this week, we have learned about more unreported deaths. The National Institutes of Health, who is with us today, following Jesse Gelsinger's death put out a far-reaching call for all investigators conducting gene therapy research to remind them that they must report serious adverse events to NIH and to the FDA. The fact that NIH received 652 previously unreported serious adverse events in response to this request is really inexcusable. Clearly, our oversight system is failing.

Our hearing today is the first step in the congressional examination of the oversight procedures and guidelines in place at the NIH and the FDA to determine whether we have adequate systems to approve and then monitor these revolutionary new gene therapy trials. If we learn that the appropriate systems and guidelines are in place, on paper, we must then ask are they working in reality. I suspect they are not. The deaths of several patients reported over the last several days and the 652 previously unreported adverse events suggest the system is not working.

All of these events trigger serious questions regarding Federal oversight of these gene therapy trials as well as adherence to the Federal guidelines that are out there on the part of the individual investigators themselves and the research community.

So much of science today, at the pace at which it is moving, is introducing new ethical questions that we as policymakers must address—ethical questions regarding the risk to patients in human experimentation in these trials and the high financial interests that are at stake as increasingly the private sector is funding such trials.

We must examine our process of informing patients—is it time for us to go back and look at what truly informed consent means

in this new era of rapidly advancing science, and what constitutes truthful and complete information to patients. We must ask if there is an atmosphere of unrealistic expectations with regard to gene therapy, and we will talk about that with our third panel. What does gene therapy truly hold as a promise for cures for diseases, and how quickly can we realize those promises? Are patients given full information regarding past adverse events as they enter these clinical trials?

My objective as we go forward is to keep the hearings balanced and to make sure that our discussion is careful. Nobody is on trial here—not the Government, not universities, not research scientists. It is clearly to everyone's advantage to put everything on the table in as quick a fashion as we can. It is tough, because every day, new information is coming out, but I am very hopeful that over the course of this morning, we can achieve a balanced and careful examination and discussion.

We know that we can learn from previous mistakes. But we do need to know what those mistakes are if we are going to learn from them and if we are going to improve the system and if we are going to move forward in this field of gene therapy.

The tragedy of Jesse Gelsinger should not result in another tragedy, and that other tragedy would be to bring a halt to this promising research. That is not the objective, and in fact, I feel strongly that we need to develop a system in which we allow this promising research to continue and to flourish. I believe it does have the potential of treating cancer and AIDS and cystic fibrosis and genetic and nongenetic diseases alike. Yet throughout, we must remain steadfast in our commitment to ensure that patients are safe, that there are adequate human protections in place, and that the research is meaningful and substantial.

With that as an overview and before turning to Senator Kennedy, let me just tell people how I would like the hearing to go forward today. We will have opening statements, then we will have brief opening remarks from our witnesses. We have three panels today, and witnesses are asked to keep their remarks to around 5 to 6 minutes in length so we can carry on a dialogue among members and witnesses. Following the witness presentations, each of the Members will be allowed to ask questions. The hearing record will remain open for individuals who would like to submit no more than 10 double-spaced pages of written testimony until February 9, at which time the hearing record will be closed.

Senator Kennedy.

Opening Statement of Senator Kennedy

Senator KENNEDY. Thank you, Senator Frist, and thank you very much for having these hearings.

As you have mentioned, this issue is of critical importance to the Nation. No other medical technology offers greater potential to provide needed cures for so many diseases, and at the same time, no other medical technology has illustrated more clearly the need to protect patient safety and to provide the opportunity for informed consent.

The tragic death of Jesse Gelsinger reminds us of the hope felt by those who look to gene therapy for a cure of their illnesses and

the need for constant watchfulness in protecting the safety of patients involved in medical research.

In many ways, Jesse Gelsinger was a typical teenager. He loved motorcycles and professional wrestling; he spent time with friends and worked at the local grocery store. Yet in one respect, he was very different from all of his friends—not because he had a rare genetic disorder, but because he had the courage to put himself at risk to test what he deeply believed to be the best hope of a cure for those with genetic disorders. Tragically, Jesse's courage led to his death.

We must do all we can to see that Jesse's sacrifice was not in vain. His hope was that someday, gene therapy would provide cures to the tens of thousands of babies born with genetic disorders every year and for the millions more affected by cancer, heart disease, AIDS and many other serious illnesses.

The promise of gene therapy is shared by thousands of patients and is daily being brought closer to reality by talented researchers across the country. Today we will hear about some of the ways in which gene researchers are making gene therapy safer and more effective than it has ever been before.

Our challenge is to see that those who volunteer to participate in gene therapy trials are fully protected from unnecessary risk. Oversight of this field should be as comprehensive as possible. In particular, when tragic events do occur, they must be reported in a timely way to the appropriate oversight agencies. We must also see that those who volunteer to serve as research subjects are fully informed of the possible risks of the treatment they are about to receive so that the consent they give is well-informed.

I look forward to the testimony of our witnesses and to working with the members of the committee to assess the adequacy of the current rules governing this extraordinary area of medical research. We are particularly indebted to Mr. Paul Gelsinger for being here today and thank him for his own courage. It is never easy to talk about this kind of extraordinary human tragedy, and we are very, very grateful to him for being willing to appear before the committee today.

Thank you, Mr. Chairman.

Senator FRIST. Thank you, Senator Kennedy.

Senator Hutchinson.

OPENING STATEMENT OF SENATOR HUTCHINSON

Senator HUTCHINSON. Thank you, Mr. Chairman.

I think Senator Frist and Senator Kennedy have outlined the issues very clearly and very well.

I just want to say, Mr. Gelsinger, that I was deeply moved as I read your testimony, and I look forward to hearing your testimony and your story.

I noted in your written testimony you say that one of the leaders in the field called your son's death "a pot-hole in the race to gene therapy," and you observe that the concern should not be on getting to the finish line first but on making sure that no unnecessary risks are taken and no lives filled with potential and promise are lost forever.

How true, and I want to join Senator Kennedy in saying that in fact your son's death was not in vain, and I think that already it has called the Nation's attention to some very great dangers. So I appreciate your courage and your willingness to come forward today.

I thank you for the hearing, Mr. Chairman.

Senator FRIST. Thank you.

Senator Bingaman.

OPENING STATEMENT OF SENATOR BINGAMAN

Senator BINGAMAN. Mr. Chairman, you and Senator Kennedy and Senator Hutchinson have outlined the issues. I thank you for having the hearing, and I thank Mr. Gelsinger and the other witnesses for being here, and I look forward to the testimony.

Senator FRIST. Thank you.

Senator FRIST. Our first panel will discuss patient safety concerns and informed consent issues in clinical research.

Mr. Paul Gelsinger of Tucson, AZ is the father of Jesse Gelsinger, who tragically passed away last September during participation in a gene therapy trial at the University of Pennsylvania.

Mr. Eric Kast of Norman, OK—welcome, Mr. Kast—is a cystic fibrosis patient who has participated in a number of clinical trials, including a gene therapy trial, in order to contribute to the search for a cure for cystic fibrosis. He currently works for Blue Cross/Blue Shield of South Carolina, where he educates medical equipment suppliers about Medicare claims. He received his bachelor's and master's degree in journalism and public relations from the University of Oklahoma. He is testifying on behalf of the Cystic Fibrosis Foundation.

Mr. Kast, again, thank you for being with us today and for your dedication in combatting a disease that we have made tremendous progress on over the last 15 or 20 years.

We will begin with Mr. Gelsinger, who will be followed by Mr. Kast.

STATEMENTS OF PAUL GELSINGER, TUCSON, AZ, FATHER OF JESSE GELSINGER, PARTICIPANT IN GENE THERAPY TRIAL; AND ERIC KAST, NORMAN, OK, ON BEHALF OF THE CYSTIC FIBROSIS FOUNDATION.

Mr. GELSINGER. Thank you, Senator Frist, and thank you members of this panel for allowing me to contribute to this hearing today.

I am addressing this committee in the hope of bringing to light some very serious concerns that I have as a result of my son's death. My son, Jesse Gelsinger, was participating in a first phase clinical trial conducted by the Institute for Human Gene Therapy at the University of Pennsylvania in Philadelphia.

Jesse was recruited to participate in the trial after being told that his efforts would benefit newborns and other children with this specific disorder—ornithine transcarbamylase deficiency syndrome—and for a myriad of other liver disorders.

Jesse did not need to participate in this clinical trial; indeed, he was told that the trial would not benefit him in the least. At the time, Jesse was doing exceptionally well on his medications, and

nothing should have prevented him from living a full and happy life.

He believed after discussions with the representatives from Penn that the worst that could happen in the trial would be that he would have flu-like symptoms for a week. He was also told that the most dangerous part of the procedure was to be the catheterization procedure by which the gene therapy would be introduced to his liver and the liver biopsy that was to be done a week later.

With the knowledge I had at that time, I was comfortable enough to send my son, just 18 on June 18, 1999, to Philadelphia alone on September 9th to participate in this clinical trial. I was scheduled to fly to Philadelphia on September 18th to be present for the liver biopsy and to bring Jesse home.

Jesse put his personal life aside, took an unpaid leave of absence from his job and accommodated everyone else's schedule to do what he did. He was excited to help. In addition, Jesse relied on my judgment in participating in this clinical trial, and I trusted this to be a well-controlled and purely ethical effort.

Less than 24 hours after they injected Jesse with the vector in an amount only one other person had ever been given, Jesse's entire body began reacting adversely. He went into a coma before I could get to Philadelphia to see him and died 2 days after my arrival, directly as a result of that gene therapy experiment. While his death has been a devastating blow to us, his example has sustained us through it all.

As you can imagine, my family and I have many concerns over what happened to Jesse. Jesse and I were told in late July 1999 that a prior patient—the patient before him—had shown a clinical improvement of 50 percent in her ability to eliminate ammonia from her system following gene therapy. At the Recombinant DNA Advisory Committee meeting in December, I discovered that no efficacy was achieved at all in this patient. We were also unaware of the severity of liver injury incurred by several patients prior to Jesse. I learned after Jesse's death that Penn had removed from the information they gave Jesse and me any reference to deaths of monkeys which had previously appeared in their documents. At the RAC meeting in December, I also learned that at least one other monkey died in a related study using the same adenoviral vector used on Jesse.

I learned that Penn neglected to follow its own and FDA's protocols when it found that Jesse had ammonia levels above the permissible limits—a clear danger sign—and yet went forward with the procedure anyway.

I learned that a pharmaceutical company had conducted experiments similar to the one Jesse was in and had obtained adverse results which, if disclosed, would have fully informed Jesse and me of the real risks in this procedure.

I had very close contact with the doctors involved until December 10, 1999, immediately following the RAC meeting. Looking back, I can see that I was very naive to have been as trusting as I was.

As serious as my concerns are with the Penn trial as Jesse's father, I have equally great concerns regarding the Federal oversight of gene therapy as an American citizen. As a result of Jesse's death, many important issues regarding gene therapy have come to

light. The number and lack of proper reporting of adverse events associated with gene therapy, the secretive nature of gene therapy research, and the motivations behind the race for results are what trouble me most.

In my own heart-and-soul search for the truth, I learned that only 6 percent of nearly 700 adverse events were reported properly to the NIH; that some companies were reporting only to the FDA and labeling reports "proprietary" in direct conflict with NIH guidelines; and that the cooperative effort espoused by the NIH was virtually nonexistent.

I learned from a former RAC member, corroborated by another witness, and from the actual minutes of the June 1995 RAC meeting that business interests had unduly influenced the FDA. At the December 1999 RAC meeting, I saw many things, some encouraging and some troubling. I saw a cooperative effort on December 9, but on December 10, I listened to the biotechnical lobby offer to "voluntarily" comply with the guidelines and the pharmaceutical companies State that everything is fine the way it is, that the FDA has everything under control.

In private conversations with an FDA director, I was told that they would like to see legislative changes to untie their hands so they could be less secretive, that they could do the right thing.

I have read that my son's death has been called by one of the leaders in this field "a pothole" on the road to gene therapy. Jesse's death was no pothole. It was an avoidable tragedy from which I will never fully recover. My concern now is that Jesse's death not be in vain, not be just a "pothole." I am not against gene therapy. I recognize that it holds so much promise for so many people. But we cannot allow what happened to Jesse to happen again.

I am not a politically sophisticated man, but neither am I unintelligent when it comes to what motivates people. I understand how important competition is in the world of business, and I can understand the temptation to influence Government. And I realize the desire of some to make a name for themselves. However, when lives are at stake—and my son's life was at stake—money and fame should take a back seat. The concern should not be on getting to the finish line first, but on making sure that no unnecessary risks are taken, no lives filled with potential and promise are lost forever, no more fathers lose their sons.

The confidence of all Americans in their Government has been so weakened that the response I get most often from my story is: "So, what else is new?" even from my other children.

The answer for me in all this is to apply Jesse's intent to the oversight and application of gene therapy—not for profit or recognition—that will come naturally—but for the betterment of all people.

Senators, please help me be able to tell my children that our Government is all that it should be.

Thank you.

Senator FRIST. Thank you, Mr. Gelsinger.

[The prepared statement of Mr. Gelsinger follows:]

PREPARED STATEMENT OF PAUL L. GELSINGER

Dear Senators: I am addressing this committee in the hope of bringing to light some very serious concerns that I have as a result of my son's death. My son, Jesse Gelsinger, was participating in a first phase clinical trial conducted by the Institute for Human Gene Therapy at the University of Pennsylvania in Philadelphia. Jesse was recruited to participate in the trial after being told that his efforts would benefit newborns and other children with his specific disorder, ornithine transcarbamylase deficiency syndrome, and for a myriad of other liver disorders. Jesse did not need to participate in this clinical trial; indeed, he was told that the trial would not benefit him in the least. At the time, Jesse was doing exceptionally well on his medications and nothing should have prevented him from living a full and happy life.

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In my own heart and soul search for the truth, I have learned that only 6% of nearly 700 adverse events were reported properly to the NIH, that some companies were reporting only to the FDA and labeling reports "proprietary" in direct conflict with NIH guidelines, and that the cooperative effort espoused by the NIH was virtually non-existent. I learned from a former RAC member and corroborated by another witness and from the actual minutes of the June 1995 RAC meeting that business interests had unduly influenced the FDA. At the December 1999 RAC meeting I saw many things; some encouraging, some troubling. I saw a cooperative effort on Dec. 9, but on Dec. 10, 1 listened to the biotechnical lobby offer to "voluntarily" comply with the guidelines and the pharmaceutical companies state that everything is fine the way it is, that the FDA has everything under control. In private conversa-

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Senator FRIST. Mr. Kast.

Mr. KAST. Thank you, Mr. Chairman, members of the committee. I appreciate being invited here to talk with you today.

My name is Eric Kast, and I was diagnosed when I was 3 months old with cystic fibrosis, so I have never known what it is like not to have CF. Over the past 10 years, I have participated in eight different clinical trials, including gene therapy.

I would like to offer our condolences to Mr. Gelsinger for his personal loss. From the perspective of somebody who has participated in gene therapy and somebody who may 1 day benefit from gene therapy, I truly appreciate what Jesse went through and what he has done—so thank you.

This morning I would like to also share with you some of the concerns that I have as a research participant. Those issues include patient safety, informed consent, and the reporting of adverse medical events. I would also like to share with you the Cystic Fibrosis Foundation's perspective on how the safety of patients and the urgent need to develop new therapies can best be met.

First, we must maintain the FDA's authority over the gene therapy trials.

Second, we should encourage the Recombinant DNA Advisory Committee to work closely with the FDA to examine the overall field and to educate the public. We urge you to identify the best balance between patient confidentiality and the disclosure, which can ensure the patient's safety.

Cystic fibrosis is a genetic disease that primarily destroys the lungs and also affects the digestive system. Also, as a direct result of CF, I now have diabetes, so I take insulin injections. Just taking care of myself and being able to breathe takes about 2 hours per day—something that most people take for granted.

Despite my problems, I know that I am fortunate. I am 33 years old, while the average life expectancy of someone with CF currently is only 32 years. When I was born, my life expectancy was only 11. Thanks to the work of the CF Foundation, that life expectancy continues to increase every year. To me, to my 5-year-niece, who also

has CF, and to the other 30,000 people in the United States who have CF, 32 years old as an average life expectancy is just unacceptable.

One of the highlights of my life was when I was 6 years old and July 3, 1974 was proclaimed "Eric Kast Day" in Indianapolis by then Mayor Richard Lugar, now one of your colleagues. Another highlight of my life, and one of the things that I am most proud of, is the opportunity that I had to participate in gene therapy trials. To date, 180 people with cystic fibrosis have been able to participate in these trials.

Right now, we are at a crossroads in the race to find a cure for myself and those with other life-threatening illnesses. We can continue with the appropriate oversight and the caution that we require, or we can let fear paralyze us into inaction. One of my greatest fears is that if we delay greatly, I may die just a year or two before a cure for CF is found. If that happens, my wife Sherry is going to have to live the rest of her life knowing that if I had just survived for one more year, we may have lived happily together for the next 30, 40, even 50 years. We really are that close, and we have really come that far.

I believe these advances are a direct result of the CF Foundation acting as an advocate for those of us with CF. Over the past several years, the Foundation has worked closely with the FDA to speed the CF drug approval process and also to plan gene therapy research. That certainly helps those of us with CF and also those who battle every day with other life-threatening illnesses.

The Foundation does believe in the urgency of drug development, but absolutely not at the risk of patients' lives. People with CF do die every day, but the safety of all patients in clinical trials is the number one concern. Patients must be fully informed of any previous problems and any potential risks.

As a precaution, the Foundation has suspended their gene therapy trials using the adenovirus. These trials will not resume until the FDA or the RAC addresses the vector safety and also if the FDA approves future clinical trials with that vector.

The FDA must be given timely information to identify these problems and to be able to inform researchers. We must also still be able to keep patient and trade information confidential. But the rules to encourage disclosure must not undermine the private sector's role, which is critical for gene therapy to go forward. Without the private sector, gene therapy will not happen.

The Foundation believes that the RAC should focus on the progress in the entire field of gene therapy and not necessarily just on the adverse events. The FDA should maintain primary responsibility for adverse events. That agency, the FDA, has the scientific and the medical staff, such as pulmonologists and pulmonary physicians, to be able to determine whether any adverse events are directly related to gene therapy or are just the natural progression of the disease process.

The FDA and the RAC could be notified simultaneously and then work together to discuss any adverse events. Both the FDA and the RAC need to have similar strict policies regarding patient confidentiality.

Once the FDA and the RAC have studied these events, at that time information could be released to the public and to the media. With proper oversight by the FDA and reporting by an informed media, we can progress with gene therapy studies.

Issues still remain for the process of informed consent. I would like to read to you part of the informed consent that I signed prior to participating in gene therapy trials at Johns Hopkins University.

"We do not know what the risks are when people are given the altered AAV virus with the CFTR gene. The altered virus could spread to other parts of your body—the consequences of this are not known at this time. There is a very small chance that the altered virus could damage the DNA in the cells of your lungs or nose. If this happened, it could put you at risk for developing cancer in the future. You will receive no therapeutic benefit from this. Side effects in humans are not known. If you should die either during or after the study, we will ask your family for permission for an autopsy."

That is a pretty clear and strong statement; I hope you would agree. I had to rely on my knowledge as a patient in the previous studies that I participated in, but I also had to put an incredible amount of trust in those physicians and scientists that I was dealing with, that they were confident in what they were doing and that they knew what the potential side effects were and that they could do something about it if I were to be affected that way.

In closing, gene therapy does provide one of the greatest hopes for my future. In this field, we must move forward, but with the appropriate caution and oversight. I battle every day with cystic fibrosis just to be able to breathe. The Foundation, the scientists, the FDA, the doctors, and now you, Senators, are my team in this battle.

All of us take calculated risks every day, whether it is getting into our cars and driving or simply coming to work. With gene therapy, I am also willing to take calculated risks.

My battle with CF is a race. Do not let me lose that race when the finish line might be just around the corner. With proper recommendations from this committee, you will be giving me the opportunity to 1 day be able to say: Now I know what it is like not to have cystic fibrosis. That is going to be a great day.

Thank you very much.

[The prepared statement of Mr. Kast follows:]

CYSTIC FIBROSIS FOUNDATION, ERIC KAST ON BEHALF OF

Thank you for inviting me to speak to you today. My name is Eric Kast. I was diagnosed with cystic fibrosis (CF) when I was three months old, so I have never known what it is like not to have CF. I also participated in a clinical trial for gene therapy.

Today, I would like to share with you my thoughts and experiences about gene therapy, and the views of the Cystic Fibrosis Foundation on regulatory oversight for gene therapy. In summary:

- Gene therapy must continue to move forward as quickly as possible as it offers me and the 30,000 others with CF a realistic hope for the ultimate cure.
- Primary oversight of gene therapy must continue to rest with the Food and Drug Administration (FDA) as they have the scientific and medical expertise to evaluate serious adverse events in the field, and FDA can best assure protections for volunteers in studies regarding safety, confidentiality and informed consent.

• Throughout its years of successful public dialogue, the Recombinant DNA Advisory Committee (RAC) has witnessed that gene therapy, while still unique, is not as novel as we once believed when we first outlined special precautions to avoid broad virus transmission to researchers. The RAC's public role is best met through strong collaboration with FDA to examine the overall progress in this field, rather than focusing on individual adverse events and potentially violating patient confidentiality, In light of recent events, as Congress and the Administration evaluate the appropriate roles for FDA and the RAC, we urge Congress to address the appropriate balance between patient confidentiality and sufficient disclosure, with knowledgeable interpretation of data, to ensure that patients, researchers and the public are informed appropriately about vital safety issues.

Living with CF

Cystic fibrosis is a genetic disease that primarily affects the lungs. My body produces thick, sticky mucus that clogs the airways and is difficult to cough up. Because of this, I am more susceptible to frequent lung infections, which will eventually destroy my airways. To fight these lung infections, I take antibiotics intravenously. CF also affects my digestive system, so I take pills with each meal to digest my food. When I was 31, I also developed diabetes as a result of CF, so I now take insulin shots.

Compared to a healthy person who enjoys close to 100 percent of lung capacity, my lung function scores are about 40 percent. Every day presents a struggle to breathe for me and the 30,000 other people in the United States who also have cystic fibrosis. Despite this constant battle, I am fortunate. I'm still alive. I'm 33 while the current life expectancy for someone with CF is only 32. In short, I have outlived my life expectancy and I am in a race against this disease. A life expectancy of 32 years is simply unacceptable.

It is not easy for me to stay healthy. Between exercise, physical therapy to clear my lungs and breathing treatments, like Pulmozyme@ to thin the mucus and albuterol to open the airways, it takes me two hours each day just to maintain my health. Approved in 1993, Pulmozyme was the first drug ever to be approved specifically for CF. However, I live with the knowledge that, any day, my health could be taken away. Two years ago, a friend of mine with CF who was 24 was healthier than I was. Six months later, he was on a waiting list for a lung transplant, and eight months after that, he was dead. This tragic story can be told time and again by those who have known someone with CF.

People such as my friend who lost his battle and my 5-year-old niece, Kelsey, who also has CF, are my motivation to participate in clinical research. Since I was 22, 1 have volunteered for eight clinical trials, including a gene therapy trial about 3½ years ago. I have participated in clinical trials near my home in Norman, Oklahoma, as well as in Maryland at the National Institutes of Health (NIH), and at Johns Hopkins University.

I have also been active in the CF community since I was six years old when I was "poster child" for the state of Indiana. One of the highlights of my life was July 3, 1974 when it was proclaimed "Eric Kast Day" in Indianapolis by then-Mayor Richard Lugar—now one of your colleagues. Another highlight of my life—and one of the things I'm proudest of—is my participation in these pioneering gene therapy studies. Growing up, I was active in every CF fund-raising event from bowl-a-ramas to swim-a-thons. However, as I got older, I was not as comfortable asking people for money. I began volunteering for research studies and gene therapy as my way to contribute to the search for a cure for cystic fibrosis.

Indeed, we are in a race to find a cure and we will achieve this only through strong medical research. We are at a crossroads in history right now. We can continue with gene therapy—with appropriate caution—or we can let fear of the unknown paralyze us into inaction. Inaction would result in the tragic loss of those of us with CF. My greatest personal fear is that a cure will come out just a year or two too late for me. My wife, Sherry, will have to live the rest of her life knowing that if I could have just made it one more year, I would have won the race and we would live happily for the next 30, 40, or 50 years. We have come that far and we really are that close for me to believe I could celebrate a 40th or 50th wedding anniversary. It is clinical trials into promising research, such as gene therapy, that will help me make this dream a reality.

The CF Foundation's Efforts to Improve Our Lives

Advancements in CF research are a direct result of the dedication of the Cystic Fibrosis Foundation which acts as an advocate for all of us with CF. The CF Foundation is committed to finding a means to cure and control this disease and to improving the quality of life for those with CF. In 1989, Foundation-supported research led to the identification of the CF gene. From then, the Foundation began to support early research toward CF gene therapy. This past year, the Foundation

supported $36 million in medical research programs to obtain a better understanding of the basic defect and to identify new CF treatments.

I strongly believe that the Foundation's ability to play a leadership role among nonprofit organizations has positively impacted and extended my life. The Foundation has advanced research and enticed outstanding scientists into the field to help conquer CF. They helped develop new treatments through strong clinical research, such as TOBIO, which is an aerosolized version of tobramycin to treat infections in the lung.

The CF Foundation's Position on Federal Oversight

The CF Foundation believes gene therapy is one of several promising research strategies to cure CF. We want the research to progress as quickly as possible because people with CF are dying every day. And, the safety of patients who participate in studies is paramount. Already, more than 180 people with CF have participated in gene therapy trials with different vectors. From these trials, we have gained insight into the encouraging safety profile of the vectors and identified obstacles we must overcome to successfully implement gene therapy as a treatment for CF.

After the heartbreaking death last fall of a young patient at the University of Pennsylvania in a gene therapy study using the adenovirus vector, the Foundation consulted with its medical advisors and asked researchers to voluntarily suspend enrollment of their patients in gene therapy trials using this vector. These trials are suspended until FDA or the RAC issue a statement on the safety of the adenovirus vector, or FDA approves an additional clinical trial protocol with this vector.

Since the Foundation first saw the promise of gene therapy, it convened multiple meetings with the regulatory and scientific communities, including FDA and researchers, to discuss endpoints in clinical trials and delivery systems to determine what was appropriate for CF.

• Primary oversight of gene therapy must continue to rest with the FDA as they have the scientific and medical expertise to evaluate serious adverse events in the field, and FDA can best assure protections for volunteers in studies regarding safety, confidentiality and informed consent.

FDA is well-equipped to examine the cause of adverse events and has the regulatory authority to halt a trial if necessary. FDA must continue to be informed of any adverse events and to evaluate them, with strong protections for confidentiality, in the context of the gene therapy field to improve the outcomes for patients and for future research.

The Foundation believes in full disclosure to patients about the risks involved in gene therapy trials. Volunteers should be informed of the benefits and risks in trials through informed consent. It is incumbent upon researchers to share with the volunteers information on adverse events that occur in the course of these trials as new patients are enrolled, while maintaining appropriate confidentiality protections.

• Through years of successful public dialogue, the RAC has shown that gene therapy is not as novel as we once believed. The RAC's public role is best met through strong collaboration with FDA to examine the overall progress in this field, rather than focusing on individual adverse events and potentially violating patient confidentiality. In light of recent events, as Congress and the Administration evaluate the appropriate roles for FDA and the RAC, we urge Congress to address the appropriate balance between patient confidentiality and sufficient disclosure, with knowledgeable interpretation of data, to ensure that patients, researchers and the public are informed appropriately about vital safety issues.

The question remains: how do we balance patient confidentiality with the need to inform people about adverse events? We believe the role of the RAC should be complementary to FDA. One suggested compromise to facilitate the RAC's goal of public oversight is to notify the RAC simultaneously with the FDA of any adverse events associated with gene therapy. To protect patients, members and staff of the RAC must abide by strong confidentiality agreements, identical to agreements in place with FDA. The RAC should then meet with FDA, researchers and medical professionals to discuss these events.

We must remember that these research studies are preliminary. Any information on adverse events must be considered not just in the context of that particular study with that patient, but in the context of all gene therapy studies with that vector. FDA is better qualified to recognize and interpret adverse events in the broader context and should retain its oversight authority.

As Congress considers the appropriate role for the RAC with regard to oversight and public disclosure of adverse events, the Foundation recommends consideration of the following.

1. It is important that adverse events be made public to empower patients and researchers to make informed decisions. However, it is imperative that any disclo-

sures ensure confidentiality in order to protect the participation by human subjects and the integrity of research.

2. It is vitally important that adverse event data be fully considered in the context of the disease the clinical trial is designed to address as well as the field of gene therapy. This must be done in a timely fashion and by highly skilled individuals who can interpret and fully analyze the adverse event. One concern that we bring to you today is that the current composition of the RAC does not lend itself to a timely consideration of these matters nor does it have the appropriate medical staff to pay attention to the level of detail necessary to make determinations relative to specific protocols. For example, the RAC does not utilize the services of a pulmonologist who is familiar with the nuances of living with an illness, such as CF, and who can distinguish between an adverse health event which is related to a gene therapy trial or one which is related to the course of the disease.

3. Finally, it is important to consider issues relative to proprietary information so that any standard which is established for public disclosure does not deter the private sector from fully participating in this important area of inquiry. A strong public/private partnership is essential for the future development of gene therapy into a life-saving treatment.

As the field of gene therapy moves forward, effective responses to patterns emerging from adverse event reports will only be possible if reports are kept confidential, considered in a timely manner by qualified medical personnel who understand the disease and its manifestations, and are provided to the public and research community in a context which empowers understanding and appropriate action. This is not the environment that exists at the present time.

With the proper context at FDA and the RAC, public information about the trial and any adverse events could then be made available to the media. The media has the unique ability to create excitement or fear and anxiety about a new frontier. Getting the full picture from both the RAC and FDA would allow the media to report about gene therapy and other medical breakthroughs without creating hype or panic. Such reporting would not prematurely drive patients away from participating in trials before they can become fully informed of all risks and benefits.

Specifically with regard to the "Proposed Actions" to amend the NIH Guidelines on gene therapy research (64 Federal Register 224), scientists are required to share "non-confidential" information regarding serious adverse events with the RAC. However, the type of "nonconfidential" information to be shared with the RAC consists of, in part, the patient's identity (which may be coded), the medical condition and the causality between the trial and the adverse event. The "Proposed Actions" must allow for the RAC to maintain the patient's confidentiality and the integrity of the clinical trial information.

Confidentiality protections are even more critical for research on people with rare diseases, such as CF, where even minimal disclosure of clinical trial information with confidentiality safeguards could result in the local community knowing which patient participated in a trial. The Foundation is concerned that a public database which includes reports of all adverse events, even if coded, could undermine gene therapy research by making information publicly available before the medical community has a chance to thoroughly evaluate it. It would indeed be tragic if efforts to encourage public discussion of the promise and risks were to stymie gene therapy.

My Experience with Clinical Trials

Fighting every day for a healthy tomorrow, the cure cannot come fast enough—for me or for the Foundation. We all recognize that research will never be without risk. Informing patients of these risks is paramount. Only then can volunteers like me make educated decisions about whether or not to participate in research.

I would like to read to you a portion of the informed consent document I signed before agreeing to participate in the gene therapy trial using the adeno-associated virus vector at Johns Hopkins University:

"We do not know what the risks are when people are given the altered AAV virus with the CFTR gene. The altered virus could spread to other parts of your body—the consequences of this are not known at this time. There is a very small chance that the altered virus could damage the DNA in the cells of your lungs or nose. If this happened, it could put you at risk for developing cancer in the future. You will receive no therapeutic benefit from this. Side effects in humans are not known. If you should die either during or after this study, we will ask your family for permission for an autopsy."

I think that is a pretty clear and strong statement. I relied on my knowledge of the research and a great amount of trust in the scientists and physicians who were confident in what they were about to do. I also had to trust recent history. When I entered the trial, ten people who had already participated in this trial had not experienced any side effects. Fortunately, I experienced no side effects either.

Some may argue that people like me cannot agree to participate in a trial, like gene therapy. They may think that signing up for a trial which brings serious risk of illness or death is more an emotional choice devoid of reason, because of our "desperation" to find a cure. On the contrary, I know what I am risking—my future with my family—and I know that I must take these risks to give my niece and the 30,000 others with CF the chance I never really had to live a long, healthy life. We are all in this together—and we win or lose together. Research is the only hope we have for beating this disease forever.

The most important issue for volunteers in a study is safety. I want to know what other volunteers have experienced in the trials and if there were any adverse reactions linked to each study. I know that numerous tests were done before I was accepted in each trial to ensure I was healthy enough to participate. If I thought that researchers were not telling me everything, I would not participate. Informed consent is just that—informed.

Another critical issue is confidentiality of medical information. However, different people have different comfort levels. I want people to know about CF, so I often share my story. However, I do not want every stranger knowing details of my health condition. Specific medical information about volunteers should only be available to researchers who are working directly with the patient. If the information were to become public, other family members or employers who might not know about the patient's health condition might use it to discriminate.

My decision to participate in a study is simply—my decision. In all of the studies I have been fortunate enough to participate in, I know the researchers had my best interests at heart and that my health was their number one concern. I have been given the option to leave a study at any time. For example, I dropped out after three months because of the downturn in my overall health, although the researchers continued to follow me. I continued to see this physician for ongoing treatment and I was never made to feel bad about that decision. The researchers have made it clear to me they would treat me for any complications and work with my local physician as needed.

For me, clinical trial participation has never hinged upon whether money is involved. I have participated in studies where I was paid and others when I was not paid. There is not enough money in the world to offset the human and emotional costs of living with CF. I chose to participate in these trials because of my desire to help others with my disease. However, I fear that if you do not pay some people to participate in trials, you may not enroll those healthier individuals who are more capable of doing the study. People who are older and healthy enough to participate are most likely working or attending school full-time and cannot leave their job without pay. My research studies have mostly been done on weekends or a day here and there during the week.

I also recognize that participating in a clinical trial will not necessarily provide me with immediate health benefits, as the research is experimental. However, I have benefited directly from in-depth examinations as I was diagnosed with diabetes thanks to blood labs required for a study.

Gene therapy must continue to move forward as quickly as possible as it offers me and the 30,000 others with CF a realistic hope for the ultimate cure. I am confident in the FDA, the CF Foundation, and the researchers that they are taking all steps necessary to ensure that clinical trials are as safe as possible and will act quickly to address new risks or halt a trial if necessary.

Conclusion

The local CF community, my family and friends in Oklahoma look to me as a role model and as a source of information and hope because of my participation in these trials. They see this as my strong commitment to a cure. When the media reports on research, I often get calls from anxious parents who are looking for hope for their child's future. Everyone, particularly those of us living with a life-threatening illness, deserves hope for the future. Gene therapy provides one of the greatest hopes for my future.

As I described earlier, I battle every day in my fight against CF. The CF Foundation, scientists, doctors, even the FDA, and now you, honorable senators, are my partners in this battle. All of us take calculated risks every day. We get into our car and drive to work hoping the driver next to us does not cause an accident and injure us. With gene therapy, patients like me must take calculated risks. We do all we can to minimize the risks—just as you would wear your seat belt to help prevent injury.

But as someone who has participated in eight clinical trials, including gene therapy, I am willing to make informed decisions, and take those risks to contribute to better treatments and an eventual cure for cystic fibrosis. My battle with CF is a

race. Don't let me lose that race when the finish line might be just around the comer. Thank you.

Senator FRIST. Thank you, Mr. Kast, and thank you both very much.

Mr. Kast, based on what you know and what the scientists have told you and what the Cystic Fibrosis Foundation believes, do you think that gene therapy will be the answer to a cure for cystic fibrosis?

Mr. KAST. I think that eventually, it will be. It has taken a long time. I believe 1988 was when they discovered the gene for CF. At that time, my personal hope was that in 5 to 7 years, we would have gene therapy available. Obviously, it has not progressed as quickly as I would hope, but at the same time, I do not think we need to risk patients' lives to speed the process up. We do have to have the proper oversight, and eventually, I truly believe gene therapy will come around and be a benefit to those, like myself, with CF as well as a lot of other life-threatening illnesses.

Senator FRIST. The issue of informed consent is a huge issue both for Mr. Gelsinger and you, and it is an issue that we are going to have to give a great deal of thought to. As a body, we have not addressed it recently, in terms of what informed consent really means and how that data is presented to patients. How information is presented is important—you read what was on paper, but what you did not say was whether they really sat down and discussed that and how they presented it to you. As one who has participated in those trials, huge biases can be introduced, and again, it comes back to reestablishing trust between researchers and patients and making sure that trust is there. Mr. Gelsinger said very clearly that the trust has obviously been lost.

Mr. Kast, you mentioned the issue of patient confidentiality with regard to disclosure A addresse events, and I quote, that "with knowledgeable interpretation of data to ensure that patients, researchers and the public are informed appropriately about vital safety issues." Do you think that the NIH or the FDA should make information public about adverse events?

Mr. KAST. I think the NIH and the FDA need to make this public in the sense of informing the media so that an informed media can report. Too often, media can create hype about an issue like gene therapy, or they can create fear. What we need to see is intelligent reporting so that it does not create that hype or fear.

In my situations with informed consent, I have been fortunate that the doctors whom I have worked with have always been able to sit down with me and go over everything, answer any of my questions. And including what I have read to you, I have also put a lot of faith in those physicians, and it is important to me to be able to sit down and talk with them and have them tell me what their experience has been with this.

Senator FRIST. You mentioned the media interpreting the data. As a physician and a scientist, I know that interpreting raw data can be dangerous, as you well know. Then the question is—you report an adverse event to the NIH or the FDA. That system, I believe, is broken, and we are going to hear more about that. But once the data gets there, do you envision the analysis and interpre-

tation of that adverse event to be the agencies' responsibility before it goes to the media and back out through the system?

Mr. KAST. I think the very first step they should take once they analyze the data and find out whether it was because of the gene therapy or was it just the progression of the disease, it needs to go to those researchers who are involved so that it can trickle down to volunteers like myself. When I go in there and risk my life and my well-being, I want that researcher to know what has happened with similar events or similar therapies and similar trials and to be able to discuss that with me.

Senator FRIST. In your clinical trials, did you feel that adequate information was given to you, based on everything that you know today?

Mr. KAST. In my experience, yes, it has.

Senator FRIST. That is fine. That gives me a sense, and there will be a lot of other questions on this very topic.

Mr. Gelsinger, you mentioned in your testimony that adverse events in prior trials were omitted from the information disclosed to you—and you mentioned several of them in your testimony—that they came out later or that you have since learned about them, but that when you signed that agreement to participate in a gene therapy trial, you did not know about them.

Full disclosure of this information would have impacted your son's decision and your decision to participate in this trial—you can comment on whether it would or would not have. From that experience, what would you suggest be done to facilitate complete and full and truthful disclosure of these potential risks to your family and to your son?

Mr. GELSINGER. I agree with Eric that it is important for the FDA and the NIH to work together on this and come up with a consensus opinion as to whether an adverse event is directly related to the gene therapy before they release it to the press, because the press does hype it up.

But Eric used the phrase "trickle down" to the patients. I believe this needs to be directly given to the patients. We have to know what is going on. If you are going to have people putting their lives in danger, they have a right to know everything, and they should be given access to the research if they want to.

I had no idea there was no success in gene therapy before my son's participation in this. Nobody relayed that information to me. I was under the impression that this worked, that this was a field that was progressing. I found out it was an experiment. We gave consent, but in no way was it informed.

Senator FRIST. Mr. Gelsinger, you stated that you learned from a former member of RAC—RAC is the Recombinant DNA Advisory Committee—and from your reading of the minutes of a June 1995 RAC meeting that, and I quote, "business interests had unduly influenced the FDA." What did you mean by that?

Mr. GELSINGER. In my conversation with this RAC member—who just happened to be from Tucson and happened to review Jesse's specific protocol and had serious concerns over it, and he made it a point to take me to those minutes, to take me to that conversation—he felt that it was totally inappropriate, and he could not believe his ears when he heard it. Why would a man as notable as

he is take me there and make it a point to bring that to my attention?

When I went to the minutes, it was not very clear what I learned in a private conversation with him. Apparently, it was a very intense moment at the RAC meeting, and the RAC members were incensed that the FDA was dropping its plan to create a database to track adverse events and share them with investigators and everyone participating in gene therapy. And under intense scrutiny from the RAC members, he made that statement.

When I came to the realization of what that meant, I was outraged—you cannot imagine—that my Government had been influenced. These guys want to own this. They do not want to share the information. They would rather have people going down the wrong path than cooperating and making this thing work faster. They want to own it. They want to have the patents. That is the only interpretation I can take from it. It is the only one I have been able to come up with, and I have looked at it from every aspect.

I want to believe that my Government is doing the right thing, and I do not have that surety.

Senator FRIST. Is your Government doing the right thing?

Mr. GELSINGER. It is doing it right now, but it was not then.

Senator FRIST. Thank you.

I have a number of questions, but I will turn now to Senator Kennedy.

Senator KENNEDY. Mr. Gelsinger, I do not want to prolong what must be an extraordinarily difficult time for you. I just have a couple of questions.

One is what advice would you give to the parents of another child who was going to undergo gene therapy?

Mr. GELSINGER. I would advise them to have an advocate with them when they sign up for a clinical trial if they are interested in participating. We need a body independent from these investigators, someone who knows everything about what they are doing, knows all about gene therapy, the clinical trial, what the prognosis is; they could be there to answer any questions and stop the investigators when they gloss over things that could be of very serious concern.

I did not have that. I guess I was not smart enough to think about it then.

Senator KENNEDY. That is a very reasonable assumption in terms of the circumstances that you are faced with.

Let me ask you what you hope will come out of this hearing. What do you want us to do?

Mr. GELSINGER. I would like to see perhaps more funding for the FDA so they can do a better job of oversight. They have expressed to me that they need more resources. I would like to see the NIH much more involved in the oversight. My understanding is that the NIH and the FDA should be working as brothers rather than as totally independent agencies. They should be working together, and apparently, that has not been happening, as evidenced by the number of adverse events that the FDA is aware of and the very few that the NIH was aware of—and they were all supposed to have the same information. That is frightening to me.

Senator KENNEDY. Mr. Kast, thank you so much for your extraordinary presentation. It was enormously powerful testimony.

You have been involved in a lot of these clinical trials. When you look over those informed consent statements, what are the things that you are looking for? What do you think is most important in there?

Mr. KAST. I think the number one most important thing is knowing what side effects other people have experienced. In most of the studies that I have been a participant in, I have been between about the 10th and 15th person to do those experiments; I have never been the first one. So I am looking for what side effects did those people who participated prior to me experience, and if they did experience side effects, were they treatable, and what was done about them. The written consent usually states all of those, every possible side effect there is, but I am also depending on that researcher to verbally tell me what his experience has been, and I think they need to know what other researchers' experience has been so they will know what to expect.

I think the researchers need to be able to talk back and forth with each other—in spite of what company is doing what research, there needs to be a mechanism in place where these researchers can find out what has happened in other similar research with other patients, and that can be discussed with the patient so that I personally know what everybody else has experienced so that I can make an informed decision.

Senator FRIST. Do you feel that over the past, in the range of different clinical trials you have participated in, that you have gotten that information? Do you find that some have been better than others?

Mr. KAST. In my situation, I have been happy with the informed consents and the information that I have been told. I have participated in studies at the National Institutes of Health and at Johns Hopkins, as well as with my own physician back in Oklahoma, and I think they have always had my best interests at heart.

Senator KENNEDY. Let me ask you this. On the issue of confidentiality, what is your sense about the extent of public discourse we ought to have in terms of the side effects, benefits, and dangers of these different treatments?

Mr. KAST. I think the public discourse should be just like what is happening here. In our situation, we are publicizing what we have done. A lot of patients do not want others in the community to know they have AIDS or cystic fibrosis or cancer or other life-threatening diseases. In my situation, I believe the more I can let people know about CF, the more people are going to understand it.

So on patient confidentiality, we have to know what is happening with this research, yet keep patients' names and specifics about the patients private.

Senator KENNEDY. Thank you.

Thank you very much, Mr. Chairman.

Senator FRIST. Thank you, Senator Kennedy.

Senator Hutchinson.

Senator HUTCHINSON. Thank you both for your very powerful testimony.

Mr. Gelsinger, how was Jesse solicited to participate in the University of Pennsylvania gene therapy trial?

Mr. GELSINGER. His specialist in Tucson, a geneticist who saw Jesse on a semiannual basis, was submitted a letter by Dr. Mark Batchaw, one of the principal investigators in the clinical trial, seeking to recruit patients.

Senator HUTCHINSON. And since you were not informed about the monkey deaths and other pertinent information relating to the virus vector gene, how did you find out that only one other person had been given as strong a dose as Jesse?

Mr. GELSINGER. I knew Jesse was in the last cohort and was going to be the second person treated in that cohort, and that was at the strongest dose level.

Senator HUTCHINSON. When did you find that out?

Mr. GELSINGER. I was aware of that.

Senator HUTCHINSON. And you stated that in your research, you found out that only 6 percent of adverse events are being properly reported to the NIH and that some companies are only reporting to the FDA, and they are labeling their reports "proprietary" so as not to make that information public.

As a matter of fact, my understanding is that the NIH learned of Jesse's death through a newspaper article, so that a very serious breakdown occurred there.

Mr. GELSINGER. I am not surprised at that at all.

Senator HUTCHINSON. Do you feel that the FDA should be required to report such adverse events whether or not they are considered proprietary, and do you think the FDA has enough authority now to address adverse an event when it has occurred?

Mr. GELSINGER. I believe the FDA should share the information with the NIH whether an event is proprietary or not. I do not think it should be released to the media unless it is determined that that adverse event was a direct result of the gene therapy.

Proprietary rights—what is more important? That is what it all comes down to to me—is human life more important than owning something? I thought this was all about the people, and I am very disappointed to find out that it is not just about the people.

Senator HUTCHINSON. Thank you.

Mr. Kast, I believe you said you have participated in eight clinical trials, and you have told us a lot about informed consent and what was involved in it. You mentioned one particular trial in which you found out that 10 people who had already been through the trial had experienced no side effects. How did you learn this information? Did you research it, or——

Mr. KAST. I asked. I think I have had enough experience participating in these trials, and I have always been involved in CF research and fundraising, and I ask the researchers. I am concerned about it, and I have had previous experience, and my experience has always been that if I ask the researchers, they have told me what they know. If I thought that they were misleading me or were not answering me fully, I would have real second thoughts about participating.

Senator HUTCHINSON. Do you have any concern that a public database in which information about adverse drug events, which was stripped of any personal identifiers, would hamper research?

Mr. KAST. I think that that is something that this committee needs to decide. From my own personal perspective, I think the researchers need to know what these adverse events are, and that needs to be told to the patients. Now, how that happens, I do not have the answer for. Hopefully, that is what this committee will work on.

Senator HUTCHINSON. In your own personal experience, have you experienced any side effects or discovered any information that was not disclosed to you?

Mr. KAST. The only what you could call "side effect" that I have had was in a local study in which I participated in Oklahoma where I was taken off the antibiotic that I normally take every day to do an experiment with a new antibiotic. It was a similar antibiotic but a different dosage, and it was a 6-month trial. After about 3 months, I knew my health was deteriorating because of it. I did not know whether I was on the real drug or on the placebo, but at that point, I took myself out of the study and got back on the medication I had been taking before, and I was okay again. So in that case and in every case, the researchers have made it very clear that I was able at any time to leave that study, and it would not be held against me. In this case, I did take myself out of that study and was still followed by that physician afterward.

Senator HUTCHINSON. So this was a side effect that they evidently were not aware of that might occur that you had not been——

Mr. KAST. To me, it really was not a side effect. I was on an antibiotic which I take every day as an inhalation treatment, and I was put on the same antibiotic but at a different dosage and a different formulation of that antibiotic, and at that point, whether it was the real thing or placebo, my health deteriorated because I was not on the previous antibiotic. At that point, I could tell—I was coughing more, I was more short of breath, I was not feeling overall as good as I usually would. At that point, I took myself out of the study, got back on my medication, and I was okay.

One thing that you should realize is that with cystic fibrosis, if I have a lung infection, it is a gradual deterioration over time. It is not like tomorrow I will have lung infection, and by next week, I will be in the hospital. This is something that happens over a period of time, so I can tell if I am not feeling good, and I can do something about it. It is not really acute but is more of a chronic illness.

Senator HUTCHINSON. Thank you, Mr. Chairman.

Senator FRIST. Thank you.

Senator Dodd.

Senator DODD. Thank you very much, Mr. Chairman, and thank you immensely for holding these hearings. I am not a member of this subcommittee per se, but I was very interested in coming by this morning to hear the testimony of these witnesses.

Let me thank both of our witnesses for being here. Particularly in your case, Mr. Gelsinger, this is a difficult day for you, but I am confident that what you are doing is tremendously valuable and helping out an awful lot of other people by being here and sharing what you have gone through with your child; so as hard as it is, there is great value in your stepping forward. And we thank you

as well, Mr. Kast, for sharing your thoughts; I found your testimony very, very compelling and very worthwhile.

Let me just follow up on a couple of things if I could. Mr. Gelsinger, I was intrigued to read about Jesse's decision to be a part of this clinical trial. The notes I have indicate that there was enough information around that this was going to potentially affect babies who were stricken with this disease, so that as I understand it—and you correct me if I am wrong—there was no potential benefit at all to Jesse directly as a result of participating in this trial. If that is the case, I would be very interested in what motivated you and Jesse to decide to be a part of this trial, knowing that he could not be a beneficiary of whatever the results were. Am I correct in that, by the way?

Mr. GELSINGER. They indicated that there may be a transient benefit to him for perhaps 4 to 6 weeks; that his liver function, his OTC enzyme, would perhaps increase had it worked, and that it would demonstrate exactly how well this therapy would work. Jesse was only 6 percent efficient in the OTC enzyme compared to everyone else at 100 percent efficiency. So the data that they would get—and this was indicated in my conversation with Mark Batchaw—actually, I made the statement, and he concurred—I said to Mark, "So, with Jesse participating, you will be able to see exactly how well this works?" And he said, "That is the hope, and it would be for the babies."

With that knowledge, there was no way we were not going to participate in this clinical trial. I mean, this was for the benefit of other human beings. It looked safe, it was presented as safe, and it was going to benefit everybody. I encouraged my son to do this. He relied on my insight. We talked it over, and he said, "Sure, Dad." He trusted me; I trusted them. And I was not given all the information, and some of the information I was given was not true.

I feel like I was led, that we were locked in. I never even reconsidered once I had that knowledge. That probably is the thing that hurts the most—that we were misled, that this was not as ethical as what was presented, and that cannot happen.

The medical profession has to be totally honest and truthful, and it has to be presented without them having an interest in succeeding at any cost, at any stake. These guys were close. They knew it, I know it. They were willing to take the risk, and we just did not know what that risk was.

Senator DODD. Do you fault the person you were dealing with directly, or was the doctor misinformed, in your view?

Mr. GELSINGER. I do not know the answer to that. I personally feel that he may have been misinformed, since Mark Batchaw does not work for the University of Pennsylvania. He is the head of The Children's Institute here in Washington, DC. He is the expert on Jesse's disease.

Senator DODD. I see. I think your point about an advocate is one that needs to be made more generally in medicine. It is always striking to me the resistance that we see. As much as I admire the medical profession, you always get the sense from talking to people that there is a sometimes unspoken, sometimes spoken, resistance to the idea of bringing someone else in to do a lot of the tough questioning that parents or patients themselves are reluctant to

bring up because of their fear that the doctor may not like them or the researcher may not like them, or may drop them. It becomes a personal decision in some ways, rather than having someone there with that cold eye who will go down that list of tough questions and ask them. So I applaud you for that recommendation. I think it is tremendously worthwhile.

Mr. Kast shared with us what other patients have shared with him since word of Jesse's death has obviously gone out, and those involved in the gene therapy community are well aware of it. I wonder what the reactions are of other patients whom you have had a chance to talk with? Mr. Kast answered that question, but I wonder if you could share with us, Mr. Gelsinger. I heard what you said earlier, and I do not take issue with anything you have said about information withheld and adverse effects not shared—but what has been the effect on the community of other patients who are involved in gene therapy? How are they reacting to the information about Jesse's death? I would ask either one of you to answer.

Mr. KAST. I think it is always difficult to get patients to participate in these trials, partially because, as Mr. Gelsinger said, there is no direct benefit at that time. I have always done these trials to help myself in the future, to help my niece, who is 5 years old, and to help other people with CF. I have always known that there will be no direct benefit to me.

So in the community—I spoke earlier about informed reporting—when we get reports that may or may not be correct, I always get calls from parents in Oklahoma— because most of the people there know me and see me as a role model—asking me about the research, and I have to try and sort through it. I have been able to call researchers at Johns Hopkins and ask them about it when I see something in the media, and they have always been willing to talk to me about it.

So I think people have looked to me as a resource, and I think any incorrect reporting by the media certainly hurts the chances of the gene therapy progressing because people are worried about getting involved in it.

In Jesse's case, if I had been told that in one of the gene therapy studies that I was about to participate in, two monkeys had previously died, I would say I am sorry—let somebody else do that research. I would not be willing to participate in something like that.

So again, it comes back to the informed consent. If patients are worried about what is going to happen to them in these studies, you are not going to have any participants willing to participate.

Senator DODD. Has that been the reaction you have heard as well, Mr. Gelsinger, from other patients or families?

Mr. GELSINGER. I have not been in communication—I have received some emails from some people and a few phone calls from other participants, but mostly they were just expressing condolences. I have not been in direct communication with other patients who have participated.

Senator DODD. OK.

Mr. GELSINGER. In Jesse's clinical trial, a lot of the people who participated were parents of children who had his disorder, mothers who had had children die from this disease, and they are pretty

desperate people, and they would be willing to step out and take that risk.

We were not in a desperate situation, and not to have the information that I should have had was just not right.

Senator DODD. Yes. You will find no argument up here on that point.

I thank you both.

Thank you, Mr. Chairman.

Senator FRIST. Thank you, Senator Dodd.

Chairman Jeffords.

Senator Jeffords. Thank you, Chairman Frist.

I want to commend you for these hearings. This has been a very moving experience from which we will learn much.

I want to extend my most heartfelt sympathy to Mr. Gelsinger for the loss of his heroic son.

I was disappointed yesterday when the acting director of NIH, Dr. Ruth Kirschstein, disclosed that only 39 of 691 adverse events associated with gene therapy similar to the one that took Jesse's life had been reported by researchers to NIH. Dr. Kirschstein noted that NIH should have recognized such a small number of reported events, 39 out of 691, as underreporting—that is an understatement in my mind.

I was also very disappointed recently with the reported comments of one Federal official whose responsibility at the Department of Health and Human Services is the protection of human research subjects. During a presentation to the American Health Lawyers Association, this official indicated that an immediate step that could be taken would be to draft a memorandum reminding all staff of their obligation to protect the rights of human subjects.

Mr. Chairman, I do not think that drafting more memoranda will do anything to protect those people who voluntarily put themselves at risk to advance causes of science. Either more needs to be done, or our current patient protections must be better enforced.

I have no questions. You have been very forthright and very compelling in the testimony you have given to us today. I want to commend you for coming forward and sympathize greatly with what you have been through.

Thank you, Mr. Chairman. It has been very, very moving testimony.

Senator FRIST. Thank you, Senator Jeffords.

Let me thank both of you. We will now move to our two other panels. I invite both of you to stay, and I want to express again my appreciation and the appreciation of the U.S. Senate for your coming forward and talking about the very best of clinical trials and the very worst. We clearly have a lot to do. You have set the stage for this discussion in a way that is very sophisticated, very mature, and it is a discussion which we have an obligation to continue and to give some answers to both of you.

Thank you very, very much. We appreciate it.

Senator FRIST. I will now ask our second panel to come forward. Our second panel focuses on the respective roles of the National Institutes of Health and the Food and Drug Administration with regard to oversight of gene therapy research.

As they come forward, I would like with unanimous consent to enter into the record at this point a letter that I received from the president of the University of Pennsylvania. It is about a 2½-page letter from President Judith Rodin, and let me just read a couple of sentences from it.

"First and foremost, I want you to know how seriously the University is approaching this matter."

"We have launched two independent reviews led by eminent scientists, and we have been and will continue to be strongly committed to cooperating fully with the FDA, NIH, Congress, and any other appropriate body as they review these issues."

In this letter, which we can make available to people here as well, there is an outline of the university's response, both what it has been doing and will do. We will enter the letter at this point in the record.

[Letter from Ms. Rodin follows:]

UNIVERSITY OF PENNSYLVANIA,
100 COLLEGE HALL,
Philadelphia, PA,
January 31, 2000.

The Honorable WILLIAM FRIST,
United States Senate,
416 Russell Office Building,
Washington, DC.

DEAR SENATOR FRIST: I want to take this opportunity to provide you with some background on our activities in support of the current investigation of clinical trials at the Institute for Human Gene Therapy ("IHGT") at the University of Pennsylvania.

First and foremost, I want you to know how seriously the University is approaching this matter. The death of Jesse Gelsinger was a terrible tragedy, and we are determined to learn everything we can about it to understand precisely what happened and what might be done to improve clinical trials throughout the University and at all institutions affiliated with us. We intend for our research programs, particularly those involving human subjects, to meet the highest standards. Nothing less is acceptable.

We have several, extensive efforts underway to achieve this goal and to respond to the important concerns raised by federal regulators. We have launched two independent reviews, led by eminent scientists, and we have been and will continue to be strongly committed to cooperating fully with the FDA, NIH, Congress and any other appropriate body as they review these issues.

The key facts to date are these: On Sept. 17, 1999, Jesse Gelsinger, an 18-year-old with a rare metabolic disease known as ornithine transcarbamylase deficiency ("OTC"), who was participating in an experimental gene therapy trial at the Institute for Human Gene Therapy at the University of Pennsylvania, died at the Hospital of the University of Pennsylvania four days after being injected with corrective genetic material for the disease. OTC is an inherited disorder that in its most common form causes death in affected newborn mates because of their inability to properly process nitrogen in food proteins due to a genetic defect in the liver. The clinical trial was voluntarily halted pending review. All appropriate regulatory agencies, including the Food and Drug Administration, which approved the trial, were notified promptly; we pledged to cooperate, fully and completely, with any agency reviews undertaken. Thereafter, the FDA began a review of the clinical trial. On Jan. 19, 2000, the FDA completed its on-site review and issued a Form 483 raising important questions about IHGT's monitoring and oversight of this and other clinical trials. Two days after issuing the Form 483, the FDA placed a hold on all clinical trials at IHGT. On Jan. 18, 2000, the Office for Protection from Research Risk ("OPRR") forwarded to us a citizen complaint with regard to the review of the OTC clinical trial by Penn's Institutional Review Board and commenced an investigation.

The University takes the FDA's action and OPRR's letter—and the questions raised about IHGT's monitoring and oversight of clinical trials -extremely seriously. A team of scientists and administrators is working around-the-clock to ensure that the IHGT provides a comprehensive, detailed and accelerated response to the FDA and the OPRR as soon as possible.

Additionally, I have initiated two separate reviews related to this matter—an independent review by outside experts and an internal review by Penn faculty—both of which will involve distinguished research scientists with a wealth of academic expertise and relevant experience.

The independent panel will be made up of senior academic leadership and renowned research scientists who are unaffiliated with the University of Pennsylvania. It will be chaired by William H. Danforth, M.D., Chancellor Emeritus and Vice Chair of the Board of Trustees of Washington University in St. Louis, and it will include Joseph B. Martin, M.D., Ph.D., Dean of the Faculty of Medicine, Harvard Medical School; Edward J. Benz, Jr., M.D., Sir William Osler Professor and Director of the Department of Medicine, Johns Hopkins University School of Medicine; Inder Verma, Ph.D., American Cancer Society Professor of Molecular Biology, The Salk Institute, La Jolla, Calif.; Rochelle Hirschhorn, M.D., Professor of Medicine and Cell Biology and Chief of the Division of Medical Genetics, Department of Medicine, New York University School of Medicine; and Daniel Callahan, Ph.D., Director of International Programs, The Hastings Center, Garrison, N.Y. They will have a broad mandate to conduct a comprehensive review of every aspect of IHGT's procedures for oversight and monitoring of clinical trials.

This committee will report directly to me; its charge follows below:

1. To conduct a thorough, independent review in order to carefully evaluate and assess IHGT's oversight and monitoring of clinical trial programs, with particular emphasis on the FDA's findings about the OTC Therapy Trial and IHGT's response to those findings.

2. To recommend any additional actions necessary to ensure the highest standards are set and met in the conduct, oversight and monitoring of future IHGT clinical trials, including a framework for University monitoring of compliance with these recommendations.

3. To report findings of review to the President of University of Pennsylvania and recommend issues to be referred to the University's faculty committee charged with reviewing human subject research.

Additionally, I have formed a committee of Penn faculty, chaired by Provost Robert L. Barchi, himself a distinguished scientist and scholar, and comprised of research scientists with a wealth of talent and relevant experience, who will conduct a proactive review of all aspects of research involving human subjects anywhere at Penn. They will examine everything we do, from the mechanics of the approval process, to oversight and the functions of our Institutional Review Board, to ultimate accountability for this research.

Again, we deeply regret Jesse Gelsinger's death, and we want to learn everything we can about how and why he died. We also want to consider everything and anything we can do to improve our oversight and monitoring procedures for essential clinical research. As I said, nothing less than the highest possible standards are acceptable. And, Penn is deeply committed to cooperating fully with the appropriate regulatory agencies and public officials examining these complex issues.

We welcome any suggestions you may have on how we are approaching this matter, and, of course, we will keep you informed of all significant developments.

Respectfully,

JUDITH RODIN
President

Senator DODD. Mr. Chairman, may we also have opening statements included in the record?

Senator FRIST. Opening statements will be made a part of the record as well.

[The prepared statement of Senator Dodd follows:]

PREPARED STATEMENT OF SENATOR DODD

Mr. Chairman: I would like to begin by expressing my sympathy to Mr. Gelsinger and his family for the loss of his son. I appreciate his willingness to share his story with us.

I would also like to thank you, Mr. Chairman, for convening this hearing to review the troubling issue of patient safety in gene therapy research.

Over the past decade the science of gene therapy has developed at an astonishing pace. In laboratories across the country research-

ers are working hard to turn science fiction into reality—attempting to engage a patient's own genes in the battle against diseases like cancer, AIDS, cystic fibrosis and rheumatoid arthritis. While we have yet to see the potential benefits of gene therapy realized, the promise that this research holds has ignited the hope of millions of individuals suffering from deadly and debilitating illnesses.

That is why it is so unfortunate that recent revelations about critical safety information from gene therapy trials being withheld from federal regulators and from patients is threatening to shatter the public's confidence in gene therapy research.

Certainly all experimental treatments, by their very nature, contain some risk, and gene therapy is no exception. Yet, despite the risks, each year thousands of patients agree to participate in clinical trials, either in hopes of improving their own health or the health of future generations. In doing so, they place their trust in the researchers and in their assurances, backed by the federal government, that patient safety is paramount.

To maintain that trust, the actions of the researchers and the vigilance of federal regulators must be above reproach. That is why even the appearance of impropriety—of researchers putting business ahead of science—is so troubling.

We should all be outraged when one of the most basic tenets of ethical research—informed consent—is violated. And we should all be alarmed by attempts to shroud information about adverse reactions in secrecy.

I deeply regret that it took a tragedy for us to focus our attention on this issue, but I am pleased that the Chairman has so quickly responded to calls for a thorough review of recent events and of the adequacy of existing mechanisms for ensuring patient safety.

I would like to thank our witnesses in advance for their contribution to our understanding of the issue of patient safety in gene therapy and I look forward to their testimony.

Senator FRIST. We have in the second panel over the last week had a change in witnesses from what we previously announced—actually in the last 3 days—and the administration's witnesses from the NIH and FDA are different than had been previously announced, at the request of the administration. For that reason, let me ask several questions for the record so we will know who you are, whom you report to, whom you represent today.

We will begin with Dr. Amy Patterson. Dr. Patterson, what is your official title?

Dr. PATTERSON. Yes, Senator. I am director of the Office of Biotechnology Activities at the National Institutes of Health.

Senator FRIST. And where is your office in the overall hierarchy of the National Institutes of Health?

Dr. PATTERSON. My office is located within the Office of the Director of the NIH.

Senator FRIST. And you report directly to whom?

Dr. PATTERSON. I report directly to Dr. Lana Skirboll.

Senator FRIST. Thank you for clarifying that for the record.

Dr. Siegel, let me do the same with you. This is Dr. Jay P. Siegel, and Dr. Siegel, your title?

Dr. SIEGEL. I am director of the Office of Therapeutics Research and Review in the FDA. This office is an office within the Center

for Biologics Evaluation and Research, which is directed by Dr. Kathy Zoon, who is my immediate supervisor. All review and regulatory activities regarding gene therapy are overseen in the Office of Therapeutics.

Senator FRIST. So you report to Dr. Zoon——

Dr. SIEGEL. Yes.

Senator FRIST [continuing]. And Dr. Zoon reports to whom?

Dr. SIEGEL. To the commissioner.

Senator FRIST. Thank you both for clarifying that information. We appreciate both of you being here today. As you can tell, we have a number of questions, and I hope that our discussion today will help begin to answer a lot of those questions as we go forward.

Let us begin with Dr. Patterson, followed by Dr. Siegel.

STATEMENTS OF DR. AMY PATTERSON, DIRECTOR, OFFICE OF BIOTECHNOLOGY ACTIVITIES, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD; AND DR. JAY P. SIEGEL, DIRECTOR, OFFICE OF THERAPEUTICS RESEARCH AND REVIEW, FOOD AND DRUG ADMINISTRATION, ROCKVILLE, MD

Dr. PATTERSON. Thank you, Mr. Chairman and members of the subcommittee.

As you have heard, I am Amy Patterson, director of the Office of Biotechnology Activities at NIH. I am honored for the opportunity to be here today to discuss NIH's role in activities related to the oversight of gene transfer research.

I wish to extend the agency's deep condolences to Mr. Gelsinger and his family.

Mr. Chairman, I would first like to say that NIH understands that our ability to support and conduct clinical research is predicated on trust. We have a profound compact with patients and their families to ensure that every measure humanly possible is taken to ensure that those trials are conducted in the safest and most ethical manner possible.

We do this through a comprehensive system of Federal laws, regulations, and guidelines that are designed to protect human subjects in clinical trials. Jesse's death is a harsh reminder that investigators must comply with these standards and principles for the safe and ethical conduct of clinical trials.

As you have already said, gene therapy is a relatively recent and still experimental application of recombinant DNA technology. It has caught the public's attention not only because of its promise, but also because of the deep ethical and societal implications that research which involves the basic unit of human life, DNA, holds.

Gene therapy may be used to provide a copy of a normal gene to directly alter or repair a mutated gene or to regulate the expression of other genes. Clinical gene transfer research has grown exponentially since the first experiment was done back in 1989. To date, more than 4,000 patients have participated in clinical trials, and over 400 trials have been performed. The vast majority of these studies are designed to assess safety and toxicity. Only one percent of the trials have progressed to clinical efficacy studies. Because of this, we feel it is more accurate to call this area of research "gene transfer" rather than "gene therapy."

Gene transfer trials target a wide range of diseases including cancer, HIV infection, cystic fibrosis, cardiovascular disease, arthritis, and hemophilia. NIH currently supports approximately 160 gene transfer trials in a wide array of disorders.

NIH's unique role in the oversight of gene transfer research reflects the public's longstanding and special concerns about this area of research and NIH's leadership in scientific innovation. NIH's stewardship over this arena of research is accomplished primarily through three tools—the NIH Guidelines involving research using recombinant DNA molecules; the Recombinant DNA Advisory Committee, otherwise known as the RAC; and public dissemination of data and information about clinical gene transfer trials.

The NIH Guidelines clearly set forth standards and principles for the conduct of human gene transfer trials. They also articulate the role of the RAC and the requirements for the submission of protocols and adverse event reports to NIH.

The RAC has several critical roles in the oversight of this arena of research. It recommends changes in the NIH Guidelines to reflect advances in knowledge of the safety and science of this field. It conducts in-depth public review of all novel gene transfer protocols, and through national policy conferences, it explores in-depth the very complex scientific, social and ethical issues that this technology has raised as it has progressed forward. These conferences have yielded very important consensus recommendations that guide the field today.

The NIH Guidelines clearly and unequivocally State that investigators must report all serious adverse events to NIH immediately. Each and every time an investigator submits a protocol to NIH, they receive a letter that restates their obligation to fulfill this requirement.

The purpose of this reporting is not for day-to-day individual monitoring or to place clinical trials on hold if need be; that is one function of the FDA. Rather, it is so that NIH can mobilize the RAC and the scientific community to bring to bear their expertise and experience to better understand the potential implications for adverse events and what those implications may be for ongoing trials as well as to help design better trials in the future.

In addition, we can initiate data collection for comprehensive and public review by RAC and ad hoc experts as necessary, and as you know, this is exactly what we did 1 day after being informed of Jesse Gelsinger's death. Reporting of serious adverse events also allows us in the long-term to recognize previously unrecognized trends that may have significant implications for the safety of patients enrolled in these trials. This entire process fosters a broad public awareness on which public trust and confidence in this field is predicated.

We recently became aware that there was widespread noncompliance with NIH's requirements for reporting adverse events. We are actively analyzing the extent of this noncompliance and the possible contributing factors for this noncompliance. Investigators have violated the Federal guidelines. Our top priority is to ensure 100 percent compliance, and we have taken four immediate actions.

First, we directed institutions and investigators involved in gene transfer research to ensure and report back to us about their proc-

esses for ensuring at their local institutions full compliance with NIH requirements. In addition, we asked them to report any adverse events which had not been previously required as required to NIH.

Second, we have established, in collaboration with our colleagues at FDA, a new process whereby we know each time a sponsor submits an adverse event report to FDA. It is important to note that this is a backup system; it allows us, if we have not received the same report, to follow up with clinical investigators. It in no way obviates the obligation of the investigators to report the same events directly to NIH.

Third, we are actively exploring additional ways to enhance our reporting requirements, and we are making sure that all pertinent information regarding the safe and ethical conduct of these trials is reported in a timely fashion to the RAC and to the scientific community and the public, this being done with full protection of patient confidentiality by the stripping of individually identifiable patient information.

Fourth, the NIH is going to be making a series of site visits to NIH-funded institutions. The purpose of these visits will be to ensure compliance with the NIH Guidelines and to examine compliance with other NIH policies, including financial conflicts of interest.

One of NIH's primary oversight responsibilities is ensuring public access to information in gene transfer research. This information has always been publicly available. At each RAC meeting, we describe any new gene transfer trials, any new adverse events reported since the last meeting, and new developments in the field. This data is up on NIH's web site. Every gene transfer protocol in addition is available to the public upon request.

We are in the process of developing a technically advanced interactive database. This database is designed to serve a variety of users—patients and the general public as well as the scientific community. It will enable people to search for specific variables, aggregate data, query, answer their specific questions about this field of research.

Finally, in order to be sure that our oversight role is as optimal as it can be, because that is what we owe patients, an advisory group is evaluating NIH's oversight of gene transfer research, and the NIH Director has specifically asked this group to develop and consider several options, among which is whether approval authority should be restored to the RAC.

In conclusion, gene transfer clinical research holds tremendous promise to treat, cure, and even prevent a wide variety of human diseases and conditions. If we are to realize this promise, investigators, funding institutions and regulatory agencies must work together to ensure that this research is conducted in a safe and ethical manner. If we are to improve the Nation's health through research, we must all work—as this meeting here today is one important step forward in assuring—in concert to protect the most important participant in clinical research endeavors—the patient.

Mr. Chairman, members of the subcommittee, this concludes my statement. NIH appreciates this opportunity to participate in this critical hearing, and I am pleased to answer any questions.

Senator FRIST. Thank you, Dr. Patterson.
[The prepared statement of Dr. Patterson follows:]

PREPARED STATEMENT OF AMY PATTERSON, M.D., DIRECTOR, OFFICE OF BIOTECHNOLOGY ACTIVITIES, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. Chairman and Members of the Subcommittee, I am Amy Patterson, the Director of the Office of Biotechnology Activities at the National Institutes of Health (NIH). The NIH's oversight of human gene transfer research is embodied in the activities of the Recombinant DNA Advisory Committee (RAC) and the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). Both the role of the RAC and the depth and breadth of the Guidelines have changed in the last quarter of a century since their inception. The public and the scientific community have benefited from NIH's oversight and stewardship. I am honored to appear before the subcommittee today to testify about the role of NIH in supporting gene transfer research and to describe to you our plans for the future.BACKGROUND

Since the advent of genetic engineering over 25 years ago, we have reaped many benefits from recombinant DNA technology. For example, recombinant DNA technology has made possible the manufacture of therapeutic proteins, such as human insulin and human growth hormone, which have widespread clinical application and benefit. Recombinant DNA technology, which has been integral in the sequencing of the human genome, also is being used to discern the genetic basis for many diseases and to design some of our most remarkable new treatments. Gene therapy is a relatively recent, and still experimental, application of recombinant DNA technology and it has caught the public's attention—not only because of its promise, but also because of the ethical and social implications of this research.

Clinical research, including human gene therapy research, is not without risk. Research is, by definition, experimental—if the outcome were known, the study would not have to be conducted. Thus, the risks associated with the experimental treatment cannot always be predicted. For this reason, there exists a comprehensive system of Federal laws, regulations, and guidelines pertaining to the protection of human subjects in clinical trials. This fall, the tragic death of Jesse Gelsinger—a young man enrolled in a University of Pennsylvania clinical study for a disorder called partial ornithine transcarbarnylase (OTC) deficiency—underscored the need for constant vigilance by researchers, by Federal agencies, and by Institutional Review Boards (IRBs) and Institutional Biosafety Committees (IBCs) responsible for the oversight and conduct of clinical gene therapy research. The NIH and the scientific community understand that the realization of the promise of clinical research in general, and gene transfer research in particular, is predicated on the public's trust—particularly the trust of the patients and families who volunteer to participate in clinical trials.

What is Gene Therapy and What is its Promise?

Gene therapy encompasses a variety of techniques directed toward therapeutic ends. For instance, gene therapy may be used to: 1) alter or supplement the function of a mutated gene by providing a copy of a normal gene; 2) directly alter and/or repair the mutated gene; or 3) provide a gene that adds missing functions or regulates the expression of other genes. The success of this technology is dependent upon not only the delivery of genetic material into the target cells, but also the expression of the gene once it reaches its target site. Both of these requirements pose considerable technical challenges. With regard to gene delivery to target cells, a variety of "vectors" have been developed to serve this purpose. Most of these vectors are disabled viruses which work by delivering genes into certain human cell types, in much the same way as ordinary viruses infect cells.

Clinical gene transfer research has grown significantly since the first experiment in 1989. Interest in this arena of research, by both investigators and patients, has grown concomitantly with our increasing knowledge about disease-related genes. It's helpful to consider the scientific exploration of gene transfer as focused in two areas: methodologies for gene delivery and gene expression and specific diseases or conditions. Initially, gene transfer trials targeted either cancer, infectious diseases or single gene disorders such as cystic fibrosis. Increasingly however, the trend over recent years in gene transfer is to tackle diseases that involve more than one gene and are chronic. Prominent examples include heart disease, inadequate blood flow to the limbs, arthritis, and Alzheimer's. There has been increasing interest in the development of a broad array of vectors that investigators can choose from in order to best target the diseased cell type. Retroviruses can only infect actively dividing cell populations, which limits their usefulness in treating diseases of the heart or brain, where the cells are not actively dividing. There is also considerable and grow-

ing interest in the use of other methods apart from viral or bacterial vectors to deliver genetic material into cells. The use of small molecules composed of RNA and DNA to directly repair the defective DNA, rather replace the entire gene, has, for example, been applied in animal studies of sickle cell anemia.

To date, more than 4,000 patients have participated in gene therapy studies. Of the 372 clinical trials registered with the NIH, 89 percent are Phase I studies are designed to assess safety and toxicity. Ten percent are Phase 11 studies which assess safety and efficacy and generally involve a larger number and a more diverse population of patients. Only 1 percent of the trials (3 protocols) have progressed to Phase III efficacy studies. Thus, most human gene therapy clinical trials have been focused on safety, rather than efficacy. For this reason, it is perhaps more accurate to refer to this technology as "gene transfer," rather than "gene therapy, " until there is more evidence for the therapeutic benefit of this technology. NIH currently supports or conducts 157 gene transfer trials for a range of disorders, including cancer and AIDS.

Gene transfer research also has raised uniquely complex scientific, medical, ethical, and social issues that have warranted special oversight by the public and by the NIH, in particular. For example, the task of introducing genes into target cells carries with it the risk of inadvertent gene transfer to reproductive cells (sperm or egg cells), which could result in genetic changes being passed on to offspring. Similarly, because we can not yet fully control the placement and expression of the transferred genetic material, gene transfer may also pose unexpected health risks to the patient. And although the vectors used to transfer genes into cells are disabled viruses, these viruses may still retain some limited ability to cause disease, thus putting the patients and their close contacts at risk. Finally, this technology also could be put to controversial uses, e.g., for the enhancement of basic human traits such as height or hair color, rather than for the treatment of disease.

NIH Oversight of Clinical Gene Transfer Research

The NIH Guidelines and the Recombinant DNA Advisory Committee (RAC), whose unique role in this class of research is defined in the NIH Guidelines, are the key tools by which the NIH oversees gene transfer research. Investigators conducting gene transfer research—either funded by the NIH or carried out at an institution that receives NIH support for recombinant DNA research of any type—are expected to comply with the NIH Guidelines. Failure to comply with the requirements set forth in the NIH Guidelines can result in the limitation, suspension or withdrawal of NIH support to the institution. NIH can also impose a requirement for prior NIH approval of any or all recombinant DNA projects at an institution. [All clinical gene transfer trials, regardless of funding source or research site, are also subject to Food and Drug Administration (FDA) regulations (21 CFR 312). The FDA has statutory authority to allow a gene transfer clinical study to proceed and, if necessary, to place a study on clinical hold in order to ensure the safety of human subjects.]

How did NIH come to play this unique role in this important arena of clinical research? In the early 1970s, scientists discovered a way to insert or recombine human and other species of DNA into bacterial genes, hence the term "recombinant DNA." This advance raised a number of serious concerns and questions among the public as well as the scientific community about the potential environmental, ecological, and infectious disease risks of this technology. Recognizing both the powerful benefits that might emerge from this research and the depth of public concern, the scientific community issued a self-imposed moratorium on recombinant DNA research and called for the formation of a national oversight body to ensure public discussion and oversight of this emerging technology. The RAC was subsequently established by the NIH and with its advice, NIH formulated the NIH Guidelines, which set forth policies and procedures designed to maximize the safety of basic recombinant DNA research.

In the 1980s, when it became increasingly apparent that recombinant DNA technology had the potential to lead to new gene-based treatments for human disease, the NIH established a subcommittee of the RAC to explore the scientific basis for and safety and ethics of so-called "gene therapy." Composed of scientists, ethicists, lawyers, and patient advocates, as well as liaison members from the FDA and the Office for the Protection from Research Risks (OPRR), among others, the subcommittee developed a new chapter in the NIH Guidelines (Appendix M). This new chapter delineated the roles and responsibilities of individual research investigators, NIH-funded institutions, IBCs, the RAC, the NIH Office of Recombinant DNA Activities (now known as the Office of Biotechnology Activities), and the NIH Director in the conduct of human gene transfer research. It also provided guidance for optimal design of preclinical and clinical research and standards for informed consent.

IMPLEMENTATION OF THE NIH GUIDELINES

The safe conduct of experiments involving recombinant DNA depends on the individual conducting such activities. In this regard, it is important to understand what the NIH Guidelines are and what they are not. The NIH Guidelines constitute an administrative framework in which safety is an essential and integral goal of research involving recombinant DNA molecules. The NIH Guidelines cannot anticipate every possible situation. The good judgment of the individuals conducting clinical research is the key essential to protection of human research subjects. The NIH Guidelines are intended to assist the Principal Investigator, the institution, the Institutional Biosafety Committee, the Biological Safety Officer, and the Institutional Review Board in determining safeguards that should be implemented. The NIH Guidelines will never be complete or final since all conceivable experiments involving recombinant DNA cannot be foreseen. Therefore, it is the responsibility of the institution and those associated with it to adhere to the intent of the NIH Guidelines as well as to its specifics. Each institution (and the Institutional Biosafety Committee acting on its behalf) is responsible for ensuring that all recombinant DNA research conducted at or sponsored by that institution is conducted in accord with the NIH Guidelines.

To this end, the NIH Guidelines require that all investigators governed by the Guidelines submit a copy of each human gene transfer protocol to the NIH. The Guidelines also delineate, among other things, the role of the RAC, the requirements for reporting of adverse events to the NIH, the role of the NIH in ensuring public access to information about human gene transfer trials, and the role of the Gene Therapy Policy Conferences.

The Role of the RAC

The RAC has several important roles in the oversight of gene transfer research—both with regard to the Guidelines themselves and with regard to public review of protocols. In light of advances in the knowledge about the science and safety of gene transfer research, the RAC can recommend changes in the NIH Guidelines to the NIH Director. Proposed changes must be published in the Federal Register for public comment before any final change is made by the NIH Director. The RAC's most visible role is, however, the public review of gene transfer clinical protocols. This public review involves an in-depth discussion of the design of the protocol, preclinical safety data, the informed consent document, and any overarching scientific, safety or ethical issues relevant to the specific protocol.

During the first five years of human gene transfer research, there were many unanswered questions regarding the safety of this research. For this reason, every clinical gene transfer protocol registered with the NIH was required to undergo public RAC review and approval. Based on its review and discussion and any necessary follow-up with the principal investigators, the RAC recommended approval to the NIH Director, who then made a final decision as to whether the protocol could proceed.

By 1995, 149 protocols had been approved by the RAC and over 1,000 patients had been enrolled in worldwide trials. Many of the potential risks that initially raised public concern had not materialized. In response to these advances in knowledge, the NIH instituted, on the RAC's recommendation, a new phase of oversight, by which only protocols deemed novel were subject to full public RAC review and approval. In making a determination whether an experiment is novel, and thus warranting full public RAC discussion, reviewers examine the scientific rationale, whether the preliminary in vitro and in vivo safety data were obtained in appropriate models and are sufficient, and whether questions related to relevant social and ethical issues have been resolved. Trials that did not present novel and/or unresolved issues were exempt from RAC review and approval and were forwarded directly to the FDA for its review.

In an effort to further expand and re-emphasize the unique role of the RAC in the public oversight of gene therapy research and, at the same time, cease RAC's duplication of the regulatory role of the FDA, in July 1996, the NIH Director proposed further changes to the role of the RAC. After careful consideration of public comment and consultations with a variety of constituency groups, including scientists, patients, and interested Members of Congress, the NIH Guidelines were revised in October 1997. Under the current NIH Guidelines, investigators are still required to submit a copy of the proposed research protocol to the NIH and to comply with all the policies and procedures, including adverse event reporting, outlined for the conduct of human gene transfer clinical research set forth in the NIH Guidelines; the RAC is still required to publicly review all novel protocols. However, the RAC no longer approves novel protocols. In addition, the RAC focuses more attention on much needed policy issues regarding the scientific basis for and safety and ethics of, emerging issues in gene therapy research, by convening Gene Therapy Policy Conferences.

Reporting of Adverse Events

A critical provision of the NIH Guidelines requires investigators to report immediately to the NIH any serious adverse event that occurs during the course of a gene therapy clinical trial. It is important to note that the requirement to submit adverse events to the NIH is not contingent upon whether the RAC does or does not have the authority to approve protocols. It is a requirement which has, in fact, remained unchanged in the NIH Guidelines since the advent of clinical gene transfer trials.

A serious adverse event is defined as any expected or unexpected adverse event related or unrelated to the intervention that results in any of the following outcomes: death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or a congenital anomaly/birth defect, as well as important medical events that may require medical or surgical intervention to prevent one of those outcomes. In the context of a clinical trial, an adverse event can occur for many reasons and not all of these are related to the treatment, per se. In human gene transfer research, many of the patients enrolled in the trial already have serious and life-threatening diseases. Thus, a serious adverse event, or even a death, during the course of a clinical trial may be the result of the underlying disease, rather than the experimental treatment.

Although the FDA also requires reports of serious adverse events in human gene therapy, the timing and scope of these reports as well as the processes by which FDA responds to this information differ from those of the NIH. The NIH's unique role in the reporting of adverse events is perhaps best exemplified in the actions it took following notification of the death of Jesse Gelsinger. The investigators performing this trial reported the death to the NIH immediately, as required, and informed the NIH that they considered the cause of death to be directly related to the gene transfer. After consulting with the FDA and the RAC Chair, the NIH immediately notified the RAC, IBCs, OPRR, IRBs, and all principal investigators conducting gene transfer research. The NIH also requested additional data on a range of preclinical and clinical parameters from every registered researcher using adenoviral vectors in clinical trials—the vector used in the study in which Jesse Gelsinger participated. Adenoviral vectors are used in one quarter of the over 372 gene transfer trials registered with the NIH. A working group of the RAC was formed immediately to conduct an in-depth analysis of the data and, if necessary, to develop guidance regarding the continued use of adenoviral vectors in gene transfer studies.

This working group carried out a comprehensive review of the safety and toxicity data gathered from over 70 adenovirus-based clinical trials involving more than 1,200 research subjects and developed a number of preliminary recommendations. They recommended that human gene transfer research in which adenoviral vectors are being used should proceed, but with greater caution. In addition, the committee identified several other important needs, including the development of vector standards and the development of specific criteria for more uniform patient surveillance and monitoring. The working group emphasized the need for the RAC to convene more conferences which address the safety and toxicity of gene transfer, and which enhance the exchange of information among researchers. The RAC will consider the working group's final recommendations and develop a report of its conclusions and recommendations regarding the use of adenoviral vectors in human gene transfer research. As necessary, following a public comment process, the NIH will incorporate any recommendations into the NIH Guidelines.

Public Access to Data on Human Gene Transfer Research

One of NIH's primary responsibilities in its oversight in this arena is ensuring public access to data on gene transfer research. Recently, a number of questions have been raised about the status of the NIH gene transfer trial database, and thus, about whether the NIH was meeting its goal of making gene transfer trial data public. First and foremost, it is important to understand that data on all 372 human gene transfer trials registered with the NIH since the inception of the NIH Guidelines are now, and always have been, publicly available. At each RAC meeting, a portion of the agenda is devoted to the presentation of clinical gene transfer trials that have been registered with the NIH and any serious adverse events that have been reported since the previous meeting. A copy of each new proposal is available to the public at all times. In fact, the NIH provides a copy of any proposal submitted to the NIH, upon request by any investigator or member of the public. In addition, the data reviewed at each RAC meeting are posted on NIH's website (www.nih.gov/od/oba/). This includes discussion of any novel protocols, a list of the trials registered, and any reported serious adverse events. The website contains core information about each of the gene transfer protocols registered with the NIH elements such as the protocol title, trial site, principal investigator, disease under study, and

vector being used for the gene transfer. This information exists now and is widely available on NIH's website.

The NIH has been working diligently to develop an interactive web-based database. The database is designed to enable users to search for specific variables, analyze aggregate data, and identify emerging trends in gene transfer research. This task has proven to be highly complex, particularly in light of the multiple audiences that are expected to use this resource. Our goal is to develop an electronic resource that both the general public and the scientific community will be able to easily access and use with regard to current information about specific protocols, including information about adverse events and developments in gene transfer research. The first phase of the database will be publicly available by the end of this year. In subsequent years, we will evaluate the first phase of the database and, as necessary, refine elements which do not meet user expectations.

Gene Therapy Policy Conferences

Another important function of the RAC, which was instituted in October 1997, is the convening of Gene Therapy Policy Conferences (GTPCs). GTPCs provide a mechanism for in-depth exploration of emerging scientific and ethical issues raised by the continuing progress of the research. GTPCs have been held on three extremely complex issues—the ethical issues associated with the use of gene transfer technology for enhancement purposes, scientific and safety questions about the use of lentiviral vectors, and the scientific, medical, and ethical issues associated with prenatal gene transfer. GTPCs help infon-n the field, the RAC, and the public about emerging issues, and they can, and indeed have, yielded important consensus recommendations that guide the field.

CURRENT EFFORTS TO ENSURE APPROPRIATE NIH OVERSIGHT AND COORDINATION WITH FDA

The NIH continues to consider new policies and procedures to appropriately ensure that its oversight of human gene transfer research is conducted efficiently and effectively. There is always need for improvement: the tragic death of Jesse Gelsinger and subsequent events have prompted a review of the role of the RAC and NIH in oversight of gene transfer research. In particular, recent events made it clear that the NIH needs to make some systemic changes to its oversight of adverse event reporting.

Re-evaluating NIH Oversight of Human Gene Transfer Research

In December 1999, the NIH Director established a working group of the Advisory Committee to the Director (ACD), NIH, to examine the current NIH framework for oversight and public discussion of clinical gene transfer research, especially with regard to the roles of the RAC and the NIH Guidelines. This charge was stimulated, in part, by growing concerns about the RAC's authority and its role with regard to protocol review.

In the recent past, as a result of differences between FDA's legislated requirement to review protocols within 30 days of submission to the Agency and the timing of quarterly RAC meetings, some novel clinical gene transfer trials have proceeded prior to public RAC review. This means that patients have been enrolled and treated prior to public RAC review. To this end, the ACD working group is being asked to recommend appropriate changes to the role and/or functions of RAC that would fully ensure that no patient is treated in a novel human gene transfer trial prior to public RAC review. The working group will consider options that have been put forth by the RAC, examine the merits of a return to RAC approval of all novel protocols, and/or propose another mechanism which would meet this goal.

The ACD working group is being asked to address three additional questions: 1) Are current NIH mechanisms adequate for coordination of its oversight of clinical gene transfer research with those of FDA, OPRR, IRBs, and IBCs, 2) Are additional NIH measures needed to minimize risk associated with clinical gene transfer research, and 3) What should the NIH role be with regard to reporting, analysis, and public discussion of serious adverse events. The working group will hold its first meeting this month and will meet again in March, in conjunction with the RAC, with the goal of submitting final recommendations to the Director, NIH, in May.

Ensuring Compliance With the Reporting of Adverse Events

The NIH's recent request to the gene transfer research community for data regarding the safety and toxicity of adenoviral mediated gene transfer revealed that many investigators governed by the NIH Guidelines have been under-reporting serious adverse events to the NIH. The adverse events that have been reported to us are quite varied both in the nature of the clinical events, as well as their cause. By and large, the events are due to progression of underlying disease, concomitantly administered drugs such as chemotherapy, or are known effects of some vectors, such as fever. We are deeply concerned about the under-reporting of serious adverse

events to the NIH, and we are taking steps to better understand and to address this problem expeditiously.

The NIH Guidelines clearly place the responsibility for reporting all serious adverse events on the investigator and the institution. In addition, every investigator who registers a protocol with the NIH receives a letter from the NIH reminding them of their obligations under the NIH Guidelines to report all serious adverse events. Even though these reminders are explicit and targeted to each investigator, they clearly have not accomplished what we intended.

According to the Guidelines, as a result of non-compliance, the NIH can suspend, limit or terminate NIH funds for the gene transfer project or for all recombinant DNA research at an institution. The NIH can choose to impose a requirement for prior NIH approval of any or all recombinant DNA projects at an institution. We can also conduct site visits to ensure institutions have the proper processes in place to comply with the Guidelines. To this end, the NIH Office of Extramural Research will undertake a series of site visits to NIH funded institutions to assess the level of understanding of NIH rules and to identify any problems associated with NIH oversight, paying particular attention to compliance with the NIH Guidelines for Research Involving Recombinant DNA Molecules, as well as to financial conflicts of interest.

We took several immediate steps. First, we sent a memorandum to institutions conducting human gene transfer research directing them to review their institutional policies and procedures for ensuring compliance with the NIH Guidelines and requested that any institution that found compliance problems notify the NIH. A copy of the memorandum was sent to IRBs, IBCs, and principal investigators at institutions conducting human gene transfer studies. We are in the process of reviewing responses to the memorandum and are following up with institutions, as necessary.

Second, the NIH and the FDA established a new process for sharing information with NIH and notified the gene transfer research community of this change in a November 5, 1999, letter. The FDA formalized the process in two new Standard Operating Procedures and Policies (SOPPs). The SOPPs, which were issued December 7, 1999, institute weekly notification to NIH of reports of adverse events and any other changes in gene therapy protocols received by the FDA. While these new SOPPs will enhance our ability to monitor serious adverse events, in no way will they diminish the responsibility of investigators to fulfill their reporting requirements to NIH.

Third, a working group of the RAC is reassessing the current requirements for the scope and timing of reporting of adverse events to the NIH, especially with respect to the current differences between the adverse event reporting requirements of the NIH and the FDA. The working group proposal will be discussed at the next RAC meeting in early March.

Fourth, the NIH, with concurrence from the RAC, is taking steps to prevent sponsors from circumventing public access to adverse event reports by labeling this information proprietary. The RAC articulated its strong objection to this practice, highlighted the importance of ensuring patient confidentiality to the greatest extent possible, and recommended changes in the NIH Guidelines to ensure public access to adverse event reports.

Finally, with regard to whether the change in the approval function of the RAC contributed to the under-reporting problem, it is important to point out that the Guidelines are promulgated by the NIH, not by the RAC. Therefore, the RAC's role in protocol approval has no bearing whatsoever on the obligation of investigators and institutions receiving NIH funds for recombinant DNA research to comply with any of the requirements set forth in the NIH Guidelines.

Without clinical research, there can be virtually no new diagnostics, new treatments or new prevention strategies to improve the length and quality of our lives and the lives of our families. Gene transfer clinical research holds promise to treat or even prevent a wide variety of human diseases and conditions. It is incumbent upon investigators, funding institutions, and regulatory agencies to ensure that such research is conducted in as safe and ethical a manner as possible. If we are to improve the Nation's health through research, we must all work, in concert, to protect the most important participant in the research endeavor—the patient.

Mr. Chairman, this concludes my statement. The NIH appreciates the opportunity to participate in the Subcommittee's review of recent events in gene therapy research and the Federal role in overseeing this promising area of research. I would be pleased to answer any questions you may have.

Senator FRIST. Dr. Siegel.

Dr. SIEGEL. Thank you, and good morning, Mr. Chairman and members of the committee.

I appreciate this opportunity to participate in this hearing concerning the safety and oversight of gene therapy. As you indicated, I am Dr. Jay Siegel, director of the Office of Therapeutics Research and Review at the FDA.

I would like to take a moment to extend my sincerest condolences to Mr. Gelsinger and his family on the death of his son.

Appropriate regulation in an area of rapidly evolving technologies and great potential benefit requires anticipating and minimizing poorly-characterized risks and balancing them against potential but unproven benefits. To this complex task, the Office of Therapeutics' scientists and physicians bring a unique combination of expertise in science, drug development and regulation.

Human gene therapies are regulated as biological therapies, and clinical research in the United States may only proceed under an authorized investigational new drug or IND application. Over the past 11 years, we have received nearly 300 such applications—55 in fiscal year99 alone.

The Office of Therapeutics encourages meeting with prospective gene therapy sponsors and investigators to discuss data, plans and regulatory requirements. Upon receipt of an IND application, FDA determines within 30 days whether to place the study on clinical hold or authorize it to proceed. Studies on clinical hold may not enroll patients.

FDA review of a new IND application for gene therapy includes review of product manufacturing and testing, animal studies, and the protocols or plans for clinical studies. FDA can and frequently does require changes in any or all of these areas to reduce the risks to human subjects.

Under FDA regulations, any adverse event that is associated with the use of the study drug and is both serious and unexpected must be reported as soon as possible, but no later than 15 calendar days after the sponsor receives the information, 7 if it is fatal or life-threatening. Additionally, any findings from tests in laboratory animals that suggest a significant risk for human subjects must be reported within the 15-day time frame.

Adverse events information not requiring expedited reporting is summarized in annual reports. The information provided in the adverse event reports is reviewed by Office of Therapeutics in the context of other information regarding the product and related products. Office of Therapeutics reviews of adverse events may lead to actions which include changing eligibility criteria to exclude patients at high risk, lowering the administered dose, increased testing of patients to detect early toxicity, changing the informed consent to disclose new toxicities, changing the investigators' brochure to inform all investigators, placing the IND on clinical hold, and taking any or all of these actions with regard to other INDs for related products.

The committee has asked us to address the investigation into a gene therapy clinical trial at the University of Pennsylvania. In 1996, before authorizing the protocol for this trial to proceed, FDA required product changes, additional animal studies, and several modifications to the clinical protocol to reduce the risks to subjects. Following Jesse Gelsinger's tragic death, concerns were raised

based on material submitted to the IND that the protocol had not been followed.

On January 19, 2000, FDA investigators issued a Notice of Inspectional Observations, an FDA Form 483, to Dr. James Wilson. The listed observations pertained to some of the following issues: documenting informed consent; implementing patient exclusion criteria; following stopping rules—the rules which ensure that the trial will be stopped if certain adverse events occur; reporting adverse events; initiating protocol changes; and submitting reports of animal deaths. FDA will further evaluate the inspection findings and the sponsors' response to determine what additional actions may be appropriate.

On January 21, 2000, based on the concerns raised regarding the adequacy of the monitoring program to protect the safety of patients, FDA determined that it would be prudent to place all other trials sponsored by Dr. James Wilson and the Institute for Human Gene Therapy on clinical hold until such concerns are adequately addressed.

FDA has worked closely with NIH and the Recombinant DNA Advisory Committee regarding gene therapy clinical research for many years and continues to do so. Recently, we have taken several actions to assist the NIH in ensuring compliance of investigators with reporting requirements, including: FDA issued a letter to all gene therapy clinical investigators and sponsors outlining and reminding them of the process for submission of materials to both the FDA and the NIH, and we implemented a procedure whereby the FDA notifies the NIH of FDA receipt of adverse event reports and protocol changes.

The Office of Therapeutics believes that education of investigators and sponsors on scientific and regulatory issues is a critical element of ensuring better patient protection. To this end, our scientists recently issued two guidance documents regarding gene therapy products, have given numerous presentations on gene therapy issues at many fora, and participate actively in efforts in the academic, medical and scientific communities to provide increased training for clinical investigators.

CBER intends to take the following additional steps to improve patient safety in clinical trials: to issue a proposed rule expanding public disclosure of information regarding gene therapy clinical trials; to continue our efforts and expand them to improve investigator and sponsor compliance through educational outreach; to increase inspectional oversight of gene therapy INDs, and to provide additional guidance for gene therapy products as technologies evolve.

In conclusion, in order that the potential of gene therapy may be evaluated and realized, it is essential that gene therapy research proceed in a manner which protects research subjects from unnecessary risk. The safety of gene therapy research is a shared responsibility. Sponsors and investigators must develop and follow sound and safe clinical research protocols and must provide appropriate information to oversight bodies which include the Institutional Review Board, the Institutional Biosafety Committee, the NIH and the FDA. These bodies in turn must perform their oversight functions well.

The Office of Therapeutics is committed to minimizing the risks of patients who participate in clinical trials of gene therapy while allowing the development of promising new experimental therapies. This endeavor presents difficult challenges. I believe we have met these challenges well in the past, and let me assure the committee that we will continue to do so in the future.

[The prepared statement of Dr. Siegel follows:]

PREPARED STATEMENT OF JAY P. SIEGEL, M.D.

INTRODUCTION

Good morning, Mr. Chairman and Members of the Committee. Thank you for inviting the Food and Drug Administration (FDA or the Agency) to participate in this hearing concerning gene therapy and the Federal government's role in the oversight of this field of medical research. I am Dr. Jay P. Siegel, Director, Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration. The Office of Therapeutics Research and Review is the office within FDA responsible for the regulation of gene therapy.

Before I begin, I would like to express, on behalf of the Administration, our continued concern that gene therapy studies be as safe as possible. As you know, when we recently discovered potential safety violations with clinical trials being conducted at the Institute for Human Gene Therapy located at the University of Pennsylvania we took rapid and appropriate action. We will continue to investigate this situation thoroughly and take appropriate action to help protect patients participating in gene therapy clinical trials throughout the country.

BACKGROUND

Human gene therapy is the administration of genetic material to modify or manipulate the expression of a gene or to alter the biological properties of living cells. Gene therapy has the potential to revolutionize the treatment of diseases that currently are incurable or have inadequate treatments. Cell and gene therapy products constitute an emerging area of therapeutic intervention that has only existed for just over a decade. The relative newness and complexity of the science of gene therapy presents considerable challenges in accomplishing product regulation. Whereas many biotechnology products consist of single purified proteins and antibodies, these novel therapies combine cells, tissues and even organs with genetic alterations, novel device delivery systems and use of specialized growth factors.

The original rationale for gene therapy was to treat genetic diseases by replacing a nonfunctional or defective gene. An example of such a disease for which gene therapy shows promise involves a genetic error that causes an individual to lack an enzyme which leads to a condition where the patient cannot mount an immune response to common infections. This disease, severe combined immunodeficiency, is extremely rare and has been also called the "bubble baby syndrome."

Currently, gene therapy studies are examining a broad range of potential therapeutic interventions, including stimulating the body's immune reaction to tumors, inducing new blood vessels in the heart to alleviate heart attacks, and stopping the replication of HIV in AIDS patients. There is also renewed emphasis on gene therapies for genetic diseases such as hemophilia A and B, and cystic fibrosis.

FDA REGULATORY RESPONSIBILITIES

Since the first human gene transfer in the late 1980's, human gene therapy products have become one of the fastest growing areas of product development under FDA oversight. In 1993, the Agency published a Federal Register notice which provided clarification that cell and gene therapies were subject to regulation under the Public Health Service (PHS) Act and the Federal Food, Drug, and Cosmetic (FD&C) Act.[1] Gene therapy products present extraordinarily novel and controversial issues associated with cutting edge medical technology, ranging from the use of mouse and human viruses to produce gene vectors (carriers of genes), to the ethical and social issues involved with the potential for gene alteration in utero and other uses which could affect future generations.

In the five-year period from 1989 to 1993, 48 gene therapy investigational new drug applications (INDs) were submitted to FDA. In contrast, from the publication of the 1993 Federal Register notice until January 19, 2000, 240 gene therapy WDs were submitted to FDA. Of those, 55 were submitted in the most recent Fiscal Year (FY) 1999. There have also been over 800 amendments (e.g., changes to the product,

[1] 58 *Federal Register* 197, October 14, 1993, pp. 53248–53251: Notice: *Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products.*

or new protocols, etc.) to gene therapy INDs submitted each year. The Agency has yet to receive the first application to license a gene therapy product.

FDA REVIEW PROCESS FOR GENE THERAPY

For any unapproved biological product that is to be tested in humans, an IND must be filed with FDA. The IND process for gene therapy is the same as it is for other biologic products. We encourage and recommend meetings between CBER reviewers and sponsors of a potential INDs for all biological products throughout the product development process in order to stimulate scientific interchange and clarify FDA regulatory requirements. Under statutory authority, FDA determines within 30 calendar days from receipt of an IND whether it is appropriate for the IND to proceed or, if necessary, to place an IND on clinical hold, in order to protect the safety of human subjects. This is a difficult task for novel therapies with relatively unknown risks.

Part of the FDA's review of the IND includes a review of the sponsor's proposed or FDA's recommended stopping rules. The stopping rules are rules in the protocol which assure that a clinical trial will be stopped if certain adverse events should occur. In addition, prior to allowing a clinical protocol to proceed under an IND, FDA frequently requires several modifications to the protocol to ensure that all known safety issues have been addressed. These might include: changes in manufacturing to ensure purity, additional laboratory testing of the product, additional animal testing of a product, exclusion of human subjects who might be at high risk for serious adverse events, additional safety testing of human subjects, lower starting doses in humans and slower escalation of doses. These modifications to the protocol are intended to lower the risk to human subjects.

As clinical data accumulate and product development continues, FDA continues to monitor the IND and may require further changes, for example, when adverse events are reported. On occasion, or when information raises concerns regarding the quality of the investigational product or conduct of the clinical trial, the Agency may perform an inspection.

In addition, CBER conducts regulatory research, as needed, to assist in the assessment of product safety. An example of such regulatory research is the development of assays to detect the presence of replication competent mouse retrovirus. The development of these assays are intended to help assure the safety and quality of mouse retroviral vectors used in gene therapies and therefore lead to marketing of safe products by many firms.

As with all IND studies, an Institutional Review Board (IRB) must review and approve such studies in advance to ensure the rights and welfare of study participants. The IRB plays a critical role in the review process, particularly in determining the continuing adequacy of protocols and with regard to its approval of informed consent forms which explain the known and potential risks and benefits to human subjects.

Although no product is risk-free, FDA's goal is to minimize the risks by assessing information on the product and conduct of the clinical trial including the safety reports it receives from the sponsors of the investigational therapy and similar therapies. It should be stressed that it is the sponsors and investigators of clinical trials who conduct the clinical trials and, therefore, they have primary responsibility to protect the safety of the patients or individuals participating in the trials. FDA helps assure that sponsors/investigators are meeting their obligations through the IND review process.

FDA INTERACTIONS WITH NATIONAL INSTITUTES OF HEALTH (NIH) AND THE RECOMBINANT DNA ADVISORY COMMITTEE (RAC)

In addition to FDA regulation, NIH is actively involved in gene therapy protocols. FDA has worked closely with NIH and the RAC regarding gene therapy clinical research for many years and continues to do so. The RAC makes recommendations to NIH on gene therapy issues (which is discussed at length by NIH in their testimony) and engages in a public discussion of scientific, safety, ethical, and societal issues related to proposed and ongoing gene therapy protocols. Also, a CBER representative is an ex-officio member of the RAC and many other CBER staff routinely participate in RAC meetings and a number of RAC subcommittees.

FDA and NIH continue to work together to optimize and streamline Federal regulation and oversight of human gene therapy research. FDA decides whether individual gene therapy protocols should proceed after evaluating the information in the IND, while NIH/RAC conducts the public scientific and ethical review and public discussion of novel applications of human gene transfer, which are carefully considered during FDA's review process. FDA and NIH meet regularly to discuss pending gene therapy issues.

The submission process for gene therapy has evolved over the years through a cooperative effort between FDA and NIH. The current process was reiterated recently

in Dr. Kathryn Zoon's letter dated November 5, 1999, which was sent to all gene therapy clinical investigators and sponsors and is posted on the FDA website at www.fda.gov/cber/letters.htm. The letter outlines the current process for submission to CBER of a gene therapy IND and any subsequent adverse event reports. It also describes how that process relates to the submission of gene therapy protocols and adverse event reports to the NIH, Office of Biotechnology Activities (OBA), formerly Office of Recombinant DNA Activities (ORDA), as required by the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). These NIH guidelines only apply to institutions with NIH-funded research. FDA regulates all research that is subject to an IND.

REPORTING OF ADVERSE EVENTS

Once the clinical trial has begun, the sponsors and clinical investigators have certain regulatory responsibilities with respect to reporting adverse events associated with gene therapy products. These requirements, which are the same as those for any new IND, specify that any adverse event associated with the use of the study drug that is both serious and unexpected must be reported to FDA as soon as possible, and no later than fifteen calendar days of the sponsor receiving the information. Any findings for tests in laboratory animals that suggest a significant risk for the human subjects must be reported by the sponsor within the same timeframe. Additionally, an unexpected fatal or life threatening experience associated with the use of the drug must be reported as soon as possible by the sponsor but no later than 7 calendar days after the sponsor receives the information. All other adverse events must be reported in an annual report.

The information provided in the adverse event reports is reviewed by FDA to determine whether additional actions are warranted to assure the safety of the study participants. Actions that might be taken by FDA, sponsor, investigator, or IRB could include:

- notifying sponsors with INDs for related or identical products about safety concerns;
- modifying the protocol to include changes in eligibility criteria, changes in dose, route, and schedule of administration of the product;
- changing the informed consent to disclose new toxicities;
- obtaining additional consent from current study participants to reflect new information;
- updating the clinical investigator's brochure;
- considering the need for new non-clinical studies; and, placing the IND(s) on clinical hold.

When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and treated with the investigational therapy; patients already in the study are taken off the investigational therapy unless specifically permitted to continue by FDA, based on the particular circumstances of each study.

RECENT ACTIONS

One of the issues that this Subcommittee has asked us to address is the case involving the death of a young patient in a gene therapy clinical trial at University of Pennsylvania. As the Subcommittee knows, this involves an ongoing investigation. In order to ensure that this investigation is thorough and effective, we are limited in the discussion we can have today regarding findings that are, necessarily, preliminary. FDA investigators have concluded an inspection at the University of Pennsylvania. Based upon the FDA investigators' findings, a notice of inspection observations (FDA Form 483) was issued to Dr. James Wilson on January 19, 2000, as is often done at the conclusion of an FDA inspection. The items listed on the FDA Form 483 represent the investigators' observations concerning potential deficiencies relating to the clinical investigation. In this case, the investigators' observations listed on the FDA Form 483 pertain to some of the following issues: informed consent; implementing patient exclusion criteria; following stopping rules; initiating protocol changes; and, submitting reports of animal deaths. Based upon the concerns raised regarding the adequacy of the monitoring program to protect the safety of human subjects, FDA determined it would be prudent to place all other trials sponsored by Dr. James Wilson and the Institute for Human Gene Therapy on clinical hold pending demonstration that an adequate monitoring program is in place. FDA will further evaluate the inspection findings and the sponsor's response to determine the significance of the observations and if regulatory or additional administrative action is necessary to achieve corrections. FDA will consider the full range of options and, if necessary, take further Agency action.

At the December RAC meeting, FDA provided a complete presentation concerning our adverse event reporting requirements, definitions and procedures.[2] This presentation, along with FDA presentations delivered at other forums, should help sponsors and investigators better understand FDA's requirements with regards to adverse event reporting. FDA's ex-officio non-voting representative was present at this meeting. FDA staff also delivered several presentations on the use of adenoviral vectors and the clinical trial at the University of Pennsylvania. The use of adenoviral vectors was extensively discussed at the December RAC meeting. At the next RAC meeting in March 2000, the ad-hoc working group will present and issue a report on the adverse events reported by investigators using adenoviral vectors. This ad-hoc RAC working group, including representatives of FDA and NIH, is working together to evaluate the relationship between adenovirus vectors and the adverse events. FDA hopes this effort may result in the improvement of human subject safety through the identification of clinical trials that may need additional monitoring.

In order to protect human subjects and also increase public knowledge of adverse events, FDA and NHi have taken steps to remind sponsors of their reporting requirements. In the letter dated November 5, 1999 (noted on page 7), FDA also included information to the clinical investigators and sponsors reminding them of their responsibilities to report adverse events.

As of December 1999, FDA has implemented two new Standard Operating Procedures and Policies (SOPP) to notify NIH when FDA has received adverse event reports and protocol changes (SOPP 9110.1—Notification of NIH/Office of Biotechnology Activities (OBA) of Changes in a Gene Therapy Protocol and SOPP 9110.2—Notification of NIH/OBA of FDA's Receipt of Adverse Event Reports to Gene Therapy INDs). These procedures can be found on FDA's website from the Manual of Regulatory SOPP at www.fda.gov/cber/regsopp/regsopp.htm.

With the number of gene therapy IND submissions increasing each year, FDA has continually evaluated its review and oversight processes, to ensure better human subject protection, to improve investigator compliance, to improve the quality of submitted protocols, and to provide additional guidance and standards to facilitate preparation of INDs. This has been done through educational outreach, conferences, meetings and policy development.

CBER staff serve as faculty for a number of educational programs for sponsors and investigators of INDs. Each year CBER gives numerous presentations on scientific and regulatory issues and policy as they relate to gene therapy and other biological product investigations.

FDA has sponsored or co-sponsored many educational outreach programs, including co-sponsoring three open public Gene Therapy Policy Conferences with NIH that discussed scientific and ethical issues, such as vector safety, and ethical considerations regarding prenatal gene therapies, and Gene Therapy Workshops with over 800 people attending each workshop. During these conferences and workshops, FDA presented information to sponsors and investigators on FDA requirements, recommendations and policies for gene therapy INDs. FDA held educational symposia at the 1998 and 1999 annual meetings of the American Society for Gene Therapy (ASGT) and will expand its symposia at the ASGT annual meeting in 2000. FDA continues to work with ASGT toward the development of standard approaches to preclinical toxicology studies and facilities standardization.

FDA also partners with many patient groups to provide regulatory and scientific support at patient group meetings. Such efforts with the Cystic Fibrosis Foundation and with the National Hemophilia Foundation have contributed to the initiation of a number of gene therapy trials for those diseases.

FDA reviews annual reports, which include data on patient accrual, adverse events, and scientific and medical reports. The Office for Protection from Research Risks (OPRR) and FDA educate the research community on issues related to protecting human research subjects. Both respond to questions from researchers, IRBs and institutional officials. FDA and OPRR co-sponsor several workshops annually for the research community.

FUTURE ACTIONS

FDA strives to evaluate and implement measures to improve the conduct of clinical studies. In addition to the actions mentioned previously, CBER intends to take the following steps to improve human subject safety:

• Plan to issue a proposed rule on the public disclosure of information regarding clinical trials of gene therapies that would provide more information on gene therapy clinical trials to the public.

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[2] The materials presented by FDA at the December 9–10 RAC can be found on the FDA website at www.fda.gov/cber/summaries.htm.

• Continue efforts to improve investigator compliance through educational outreach for sponsors and investigators.
• Enhance regulatory research to improve product safety.
• Provide additional guidance for gene therapy products to build upon existing guidance. In this last regard, CBER issued two guidance documents, "Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy" and Draft Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector-Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors."
• Conduct more inspections to increase oversight of gene therapy INDs.
• Encourage sponsors to assess or reassess the adequacy of their monitoring program and to consider obtaining independent monitoring as needed to improve the conduct of their trials and help ensure timely and accurate reporting to oversight bodies.

CONCLUSION

In the area of gene therapy, it is clear that many exciting innovations are emerging. While many of these new gene therapy and biotech products may yet have unknown risks, they also have the potential for tremendous patient benefit. When developing these new products, sponsors of clinical trials must accept responsibility to ensure that participants are not exposed to known unreasonable risks and that the experimental products are as safe as possible. I have outlined FDA's role in this process and have briefly mentioned our interactions with NIH. It is critically important that sponsors and investigators who conduct the clinical trials take the responsibility to assure the safety of their human subject participants. They must achieve this by using quality controlled experimental products, by practicing good clinical medicine and also by communicating accurate information to FDA regarding safety in a timely manner, as required by our regulations.

CBER is committed to minimizing the risks to human subjects who participate in clinical trials, including gene therapy studies, while encouraging the development of promising new experimental therapies. We will continue to work closely with NIH and others as appropriate. It is essential that FDA continue to develop the strongest possible science base so that our reviewers possess the necessary scientific and medical knowledge to effectively review and evaluate new and increasingly complex investigational biological products such as gene therapy.

We know that these issues present new and difficult challenges. I believe we have met these challenges in the past and let me assure the Committee that we will continue to do so in the future.

Senator FRIST. Thank you, Dr. Siegel, and thank you both. Again, this is a very important panel, because the oversight rests with the NIH and FDA, and the breakdown is apparent from the first panel, so there are many things we need to pull together over the next several minutes.

In the big picture, Dr. Siegel, how many gene therapy or gene transfer trials are ongoing now? You said 300 INDs. Could you just walk us through that?

Dr. SIEGEL. We have received nearly 300 applications. Currently, 212 INDs are active. Some of those applications, however, have more than one trial. They are the same product, and they are in the same or a closely related disease, or they would not be in the same IND. I do not have the exact number of trials.

Senator FRIST. So 212. Are they underway? When you say you have received the applications, how far along are they?

Dr. SIEGEL. Yes, the INDs are active. That means that they are not on hold; they are authorized to proceed. Many or most would be enrolling patients—not necessarily all—some are paused for various reasons.

Senator FRIST. Of that 212, how many applications are on hold or for various reasons, you have said no to?

Dr. SIEGEL. I do not have that number. I can tell you that it is very common with perhaps many or most applications as we initially see them, that we have concerns that potentially could lead

to clinical hold. Now, under regulations, in that 30-day period, we will work with the sponsor, and we may say if you lower the dose, or if you exclude patients who have this type of kidney problem, we will not need to put you on hold, and work that out. Sometimes it takes longer, and they are placed on hold. But many of the protocols go on hold ultimately as the date are generated.

Senator FRIST. And looking at potential increases 2 years from now, if you could project this out, how many do you think there will be?

Dr. SIEGEL. I was looking at the curves. I know that for my office as a total, which is largely regulating biotechnology, the growth rate of review workload for the last 5 or 6 years has been at 20 percent per year. So it has more than doubled over 5 years. And the growth in gene therapy applications appears to be at a similar rate, although there are some years when it grows more rapidly and others when it does not.

Senator FRIST. And Dr. Patterson, did you say 116 or 160——

Dr. PATTERSON. One hundred sixty NIH-funded or supported clinical trials. NIH has received over the 10 years that gene transfer research has been under way about 370 protocols. We classify them a bit differently than FDA does. As Dr. Siegel explained, an IND may encompass several clinical trials using the same product for a variety of clinical indications. We tend to classify each trial as a separate entity. There may be different principal investigators in charge of each clinical trial.

Senator FRIST. And of these 160 trials—have you seen all 160 of them? Are both of you talking about the same groups or populations?

Dr. PATTERSON. Yes.

Dr. SIEGEL. Yes.

Senator FRIST. Then, why do you have 212, and she has 160?

Dr. SIEGEL. You are talking about those that are NIH-funded?

Dr. PATTERSON. Right. Again, over the decade of history, we have had 372 trials, and at present, there are 160 actively funded NIH trials. There is a difference in the way that NIH counts or tallies trials compared with FDA. As Dr. Siegel said, an IND or investigational new drug application may encompass a number of trials, so his numbers would be bigger.

Senator FRIST. What I am reaching for is are both of you looking at every gene transfer trial?

Dr. PATTERSON. Yes.

Senator FRIST. Both of you at some point see every trial, whether it is NIH-funded or not. If it is not NIH-funded, do you see every gene therapy trial?

Dr. PATTERSON. We see all trials that are conducted either at an institution that receives any NIH moneys for recombinant DNA research. So anybody who is doing molecular biology, we see their trial. And that certainly includes the smaller subset of NIH-funded trials.

Senator FRIST. So people are slipping through the cracks, and we have got to minimize this. So every gene transfer clinical trial, both of you see; is that correct?

Dr. SIEGEL. Well, speaking for the FDA, any that is conducted in the United States, we would see.

Senator FRIST. Dr. Siegel you would see it. And I understand that if it is at an institution that receives Federal moneys, Dr. Patterson you are going to see it. My question is are there gene therapy trials that are not conducted at those institutions that are not NIH-funded that you would not see?

Dr. PATTERSON. You would have to call on my colleagues at FDA to answer that question.

Dr. SIEGEL. I do not have awareness of that, but I cannot give a definitive answer.

Senator FRIST. As we struggle to make sure that what both of you are doing, which are two different things, and both of them are important, we need to have that information. So if you could provide that at some point—I understand you do not have it now—but again, it may strike at the heart of one of the problems we have today.

Let me go specifically to some of the questions. Dr. Siegel, the FDA in its Notice of Inspectional Observations, which you mentioned, the Form 483, cited 18 observations of initial findings against the researcher involved in the clinical trial that resulted in the death of Jesse Gelsinger. You said the FDA had reviewed 20 amendments to the original protocol of that trial and had communicated by phone or fax with the researchers 50 times in the past 2 years. Given the amount of contact that the FDA and the researchers had—it sounds like a lot, but put it in perspective for us—did these 18 observations, which are pretty dramatic, escape notice of the FDA for a long period of time before you put them on paper in this form? It sounds like you were making contact throughout, and all of a sudden, these 18 observations come forward, and the researcher gets them at a fairly recent date. Where is the breakdown?

Dr. SIEGEL. Yes. I would say that the materials in those 18 observations were not materials that came to our attention as part of the communications you cited, which were communications regarding how to handle the protocol, how to deal with adverse events, and how to proceed as the protocol moved on. Those observations, as I characterized and as you can see before you, deal with operations at the university regarding the trials, regarding meeting reporting requirements, regarding following protocol, that were events that did not come to our attention until recent months.

Senator FRIST. Would the FDA have done anything differently—looking back from where we are today, given the information that was provided to you, or in terms of the oversight you should have given to the university, would the FDA have done anything differently?

Dr. SIEGEL. Well, much of that information comes to attention only through inspection. Those are inspectional observations, and most or much of that information would not be possible to generate through our normal regulatory review process of written materials. When we have the written materials, all we have to go on is what is said or written to us.

Senator FRIST. And an inspection occurs when?

Dr. SIEGEL. The vast majority of FDA inspections are done at the time of application for product approval. It is at that point that we

do oversight or inspections to ensure that the data in the application are indeed what they purport to be.

Senator FRIST. Does that system work?

Dr. SIEGEL. I think that system works very well for the materials that are in applications. I think that our inspectional program regarding experimental studies—in experimental studies, we do a very limited number of inspections largely on a for-cause basis. I think we would like to be able to do more.

Senator FRIST. So the FDA, based on what you have said, would like to be able to do more inspections. The restriction on number of inspections that you do today is what?

Dr. SIEGEL. Well, it is a resource issue. Inspections are resource-intensive. Inspections are prioritized. I think we will shift our priorities somewhat here, and it is our intent to move more resources into inspections at the investigational stage, but when a product comes to marketing and is potentially available to much larger numbers of Americans, that is, of course, a critical point and where the bulk of resources are and where we need to devote resources.

Senator FRIST. How many people are involved in this aspect of your monitoring process? How many staff are assigned the direct responsibility of monitoring these trials?

Dr. SIEGEL. Are you talking specifically about inspectional activities, or are you talking about review and oversight activities?

Senator FRIST. Let me ask about both. We have 212 trials out there. Once they are underway for monitoring, which obviously is critical, how many staff, just roughly?

Dr. SIEGEL. My office has in the neighborhood of 250 scientists—that number actually also includes some support staff but is predominantly scientists and physicians.

Senator FRIST. And they cover the 212 trials plus others?

Dr. SIEGEL. Right. We cover a broad variety of biotechnology—about half of that number I would estimate are in part in involved in gene therapy review and oversight, but that may not be all that they do. I think gene therapy, in terms of the number of active trials, is about 20 percent of the total number in my office.

Senator FRIST. And then, the inspection component of it—I assume that is the same group of people—how many there?

Dr. SIEGEL. Well, actually, only in part. Inspectional activities in the FDA are coordinated by our field office, our Office of Regional Activities, which has offices in different cities around the country that conduct inspections. However, the headquarters review staff that I just spoke of is actively involved in two ways. In all cases, we communicate with the inspectors about the issues of concern and areas to look at and help plan the inspection, and in several cases, including the case at the University of Pennsylvania, a headquarters inspector will go along; but still, the primary inspecting team is from the field office.

Senator FRIST. Thank you. That is helpful. I do not mean to push the numbers so much, but in terms of resources and your limitations and staff in a field that is growing tremendously as we project ahead, obviously that has huge implications for us.

Chairman Jeffords.

Senator Jeffords. Thank you, Mr. Chairman.

This is obviously a very disturbing hearing, and I would like to pursue your knowledge in regard to some matters.

As you know, yesterday, Dr. Kirschstein disclosed that only 39 of 691 adverse events associated with gene therapy had been reported. Today's New York Times reports that 691 adverse events have been reported to NIH.

Dr. Siegel, of these, how many have already been reported to the FDA as against the information we received?

Dr. SIEGEL. Well, Dr. Patterson's office and my office have attempted to address that question. We have not looked at the total number, but we have taken a sampling of IND files to try to get reliable estimates of where the problems and what the problems are.

If you look at total adverse events that were reported—I think this is somewhere in the 30's, numbers of INDs—if you look at total adverse events that were reported either to the FDA or to the NIH, about 95 percent of them were reported to the FDA. So there is a relatively limited number of events reported to the NIH or to the FDA.

What I do not know with certainty yet is whether any of those events were of a type that by our regulations require FDA reporting. It is important to note in this regard that the requirements for what events need to be reported to the FDA have not been identical to the requirements for what events need to be reported to the NIH.

Senator JEFFORDS. Dr. Patterson, how will NIH analyze all these reports, and what will you do with the data?

Dr. PATTERSON. First, I would like to set the record straight if I may, sir. The 691 serious adverse events that were reported encompass—because NIH Guidelines require any serious adverse event, whether it is related or unrelated to the protocol, expected or unexpected—if an adverse event occurs in a patient while he or she is enrolled in a clinical protocol, the current Guideline requires that that event must be reported immediately. So in our preliminary analysis of the 691 events, most of these events are by and large due to the patient's underlying disease. As you probably are well aware, the majority of gene transfer trials are conducted in patients with severe diseases such as advanced malignancies, and the majority of the events that we have received reports of indicate the progression of a patient's underlying disease, a side effect of a medication such as chemotherapy.

We are in the process of conducting an in-depth analysis of those adverse events in collaboration with our colleagues at FDA, and to date, we have seen no evidence that a heretofore unrecognized problem in gene transfer research is among those reports. But nonetheless we take very seriously the duty of looking through those reports and making sure.

Senator Jeffords. Are you aware or can you tell me when the information that Dr. Kirschstein reported became available?

Dr. PATTERSON. When the 691 adverse events were reported?

Senator Jeffords. Yes.

Dr. PATTERSON. Those events were reported in response to an NIH call to all investigators in the field using adenoviral vectors, the same vector that was used in the University of Pennsylvania

trial. That call for specific safety and toxicity data was issued on October 1st, and those reports came in in October and November of last year.

It is also important to remember that those 691 adverse events represent a 7-year cumulative history of the use of adenovirus. They are not events that occurred in 1999.

Senator Jeffords. They occurred over 7 years?

Dr. PATTERSON. Over a 7-year period. The first adenoviral trial was performed in 1993.

Senator Jeffords. What is the requirement for reporting an adverse reaction? Is there no time requirement—it is just whenever you feel like it?

Dr. PATTERSON. No, sir. The guideline says immediately. That is not stated any more specifically, and that is one of the things that we are clarifying, what is the scope of the reporting and what are the time lines. But the current guideline reads: "Investigators must report any serious adverse event immediately."

Senator Jeffords. Dr. Siegel, how does FDA get involved with ensuring that these reports are timely?

Dr. SIEGEL. FDA regulations call for serious and unexpected adverse events associated with the use of the drug to be reported as soon as possible, but no later than 15 days, and for fatal and life-threatening events to be reported within 7 days. I believe the time lag is to allow time as might be necessary to check the facts and collect appropriate information. That is for the written report. On serious and life-threatening illnesses, we also require essentially an immediate telephone notification.

Senator Jeffords. It is my understanding from Dr. Kirschstein that the 691 were only recently revealed, and they did not all happen last year, I presume, so what is the proper—what should have happened is the question.

Dr. SIEGEL. Well, again, recently revealed to the NIH—apparently, that comment was regarding the NIH requirements for reporting. As I said in response to an earlier question, we reviewed a subset of those to determine whether in fact we had been receiving reports. You have probably read in the press about many of the investigators saying: Well, I knew I had to report to the FDA, but I did not realize I had to report to the NIH. We wanted to check to make sure the FDA had been receiving those reports, and indeed, as I indicated, with a small number of exceptions, it appears that we have been.

Senator Jeffords. Let me understand. You are saying that they had been reported to you, the 691?

Dr. SIEGEL. Yes—well—yes. In the set that we looked at, the large majority, probably on the order of 95 percent of events reported, were reported. We did not look at all of those 691 adverse events to check reporting. Again, though, there is not necessarily an FDA reporting requirement for all of those, as our reporting requirements are somewhat different from those at the NIH.

Senator Jeffords. She disclosed that, and I am quoting, "only 39 of 691 were reported." I am sorry, I am confused. They were all reported, but nobody——

Dr. SIEGEL. There are two reporting mechanisms. You are asking about what was reported to the FDA, and I am responding to that.

Dr Kirschstein's comment is about what had been reported to the NIH and the RAC.

Senator Jeffords. Dr. Patterson, can you clarify that?

Dr. PATTERSON. Yes, Senator. Again, the 691 adverse events are the whole universe of adverse events that happened in adenoviral trials, and that is a different requirement than the FDA requirement, which is unexpected and related to, or possibly related to, the intervention for immediate or expedited reporting.

The 39 events referred to in Dr. Kirschstein's letter are those events that were reported to NIH immediately—in other words, in the time frame that we require. That is not to say that many of the other 652 adverse events—we had seen many of them previously, but they were not reported in a timely fashion. So I would like to set the record straight that it is not that NIH did not see the other 652 or a subset of them; it is that they were not reported in a timely fashion to the NIH.

Senator Jeffords. I am concerned, because as you know, we are working on the Patients' Bill of Rights, trying to expand the availability of clinical trials, and people clamor for them, especially if it is the only hope they have. I would just like to be reassured that the information will be available so that a more accurate decision can be made as to whether to participate.

Dr. SIEGEL. Let me clarify my answer, too. I stated that we do not require the same events to be reported. I should clarify that. The FDA requires all adverse events to be summarized in an annual report. I was speaking to the issue of whether they are serious and unexpected had to do with the 7-day or 15-day reporting requirements.

Senator Jeffords. Thank you. We will be pursuing this with you. Thank you, Mr. Chairman.

Senator FRIST. Thank you.

With all this concentration on numbers and reporting, I do not want to put too much or too little emphasis on it, but it does get down to trust, accountability, and where the breakdown is. We have not talked very much about the research component and their not reporting things to you, and I do want to get to that. But let me just go through it one more time.

In terms of the 200 or so trials, from the FDA's standpoint, in gene transfer trials, how many people have died?

Dr. SIEGEL. The only case where we have a definitive determination that a patient has died as a result of—not definitive, but a determination where it appears that a patient has died directly due to the administration of the gene therapy vector—is the case of Jesse Gelsinger.

However, to understand the implications of that statement, there is a lot more that needs to be said. First, most gene therapy trials are done in people with life-threatening, often terminal, illness. In fact, the majority to date have been in advanced cancer where there are no available alternative effective therapies. Patients in those trials die, and it is usually not possible to make a definitive determination. It may well appear that the death is due to progression of the cancer, and probably in most cases is—maybe in all the cases—but one cannot make a definitive determination as to

whether the therapy may have in some way increased that likelihood.

Senator FRIST. I understand exactly, but in the best estimation of the FDA, the fact that somebody was in a clinical trial accelerated the death in only one individual in all the gene therapy trials you have seen?

Dr. SIEGEL. Well, the other proviso I would put on that is that in many of these trials, gene therapy is used in conjunction with other modalities of therapy, surgical modalities and drug modalities. There have been some deaths which have occurred around the time of treatment which have raised questions as to whether or not there might be a relationship to the treatment in general, although I would say not specifically to the gene therapy product.

Senator FRIST. OK. So in essence, one death. I understand. As a physician——

Dr. SIEGEL. I understand that you understand this; I want to make sure——

Senator FRIST. In the best estimate of the experts in the United States of America at the FDA, there has been essentially one death.

Now let us move to the National Institutes of Health, again, another body that is responsible when we are talking about these reports. In the 200 or so gene transfer therapy trials, how many people have died as a direct result of participating in those trials?

Dr. PATTERSON. One patient, Jesse Gelsinger, we believe died as a direct result of his participation in a gene transfer trial. That is one patient out of over 4,000.

Senator FRIST. The deaths that have been in the media lately—for example, a death at the Beth Israel Deaconess Medical Center of a 74-year-old woman with colon cancer which had spread to other organs—again, a fatal disease, the colon cancer itself—8 hours after infusion of gene-altered cells that were meant to attack her cancer, she fell ill and subsequently had gastrointestinal bleeding and died. Where do you put that sort of case?

Dr. SIEGEL. I can tell you that those deaths were reported to the FDA. They were discussed at great length and considered both among FDA reviewers and between the FDA and the sponsor. I think that that falls into the category I was discussing before, that there are deaths which occur in gene therapy trials, as in any clinical trials, where one cannot make a definitive determination ruling in or out.

Often, as research continues, patterns emerge; as controlled research occurs, one can look at survival with treatment compared to without a treatment. So we do not put aside any of these adverse event reports, and we do not make definitive final determinations at the time except in those cases where things are clear-cut. The determinations we make instead are, though, important ones—should the trial continue; should the dosage be changed; should certain patients be excluded; should informed consent——

Senator FRIST. Yes, I understand. The big thing is that we have to be assured and must assure the American people that when we are talking about death, there is adequate reporting, and there is communication between the two of you, and appropriate actions are

taken. We saw earlier this morning that there has been a huge failure in that regard, and I think we are getting there.

Going back to what the chairman talked about, we had these things occurring over 7 years—adverse reactions, some serious, some not so serious. They have been occurring out in the field in various clinical trials. A letter goes out saying that the guideline is that you report everything to us, and all of a sudden, you have hundreds sent in. That is not reassuring, because all this is going on, and you are not aware of it, and I guess my question is why weren't you aware of it, and if you were aware of it, why did it take a death to bring it to your attention. And I guess, third, does that mean that our individual investigators out there are being irresponsible or trying to hide something from the NIH in not reporting to you? Again, 7 years with no reporting, and all of a sudden, a letter goes out saying the guideline has been on paper, the guideline is out there, you are supposed to be reporting, and all of a sudden, one group of researchers, the adenovirus researchers, report. Why?

Dr. PATTERSON. I think it is important to realize that many of those adverse events had been previously reported. They may not have been reported immediately as required. I think the death of Jesse Gelsinger galvanized the scientific community to bring to bear its experience and expertise so that we could fully understand any lessons that Jesse's death holds for the use of adenovirus vectors in particular and for the field in general.

The NIH Guidelines are quite clear in their statement that investigators must report, and again we send, every time we have contact with investigators when they submit a protocol, their obligations.

Senator FRIST. So why aren't they doing it? Why aren't they reporting these?

Dr. PATTERSON. We are undertaking now an extensive analysis to look into the extent of the noncompliance and the possible contributing——

Senator FRIST. But are you not notifying them—if I am an investigator sitting out there, and I know that the NIH requires and clearly requires me to report adverse events—which we all know what they are—is it a breakdown with the NIH? Is it a letter that goes out? Is it buried in a huge document, all the paperwork that the investigators have to put up with? Is it one sentence in there? Either you are failing to tell them, or they are trying to hide something from you that you demand. We are just trying to figure out where it is.

Dr. PATTERSON. First let me say that we find the current noncompliance not acceptable, and we will do everything we can to address it and work with the subcommittee.

That being said, to answer your question, the letter that investigators receive is a personally addressed letter that says quite clearly—a whole paragraph is devoted to the obligation and the responsibility of investigators to comply with the standards for the safe and ethical conduct of gene transfer research and in particular, it unequivocally states their obligation to report serious adverse events to the NIH. And again, we will be looking very closely

into the extent of noncompliance and taking every step to make sure there is 100 percent compliance.

Senator FRIST. I have the sentence before me that you have in the NIH Guidelines. Is there only one sentence in the Guidelines? How big are these NIH Guidelines? It says "NIH Guidelines," and this is Appendix M7-C, and it states one sentence: "Investigators who have received approval from FDA to initiate a human gene transfer protocol must report any serious adverse event immediately to the local institutional review board," and so forth, and that is the end of the sentence. Is that the only place where it says it?

Dr. PATTERSON. No. The NIH Guidelines is a lengthy document and applies to a wide variety of recombinant DNA research. Appendix M is the chapter that directly addresses human gene transfer clinical research and is just a few pages long.

The responsibility of institutions, the institutional review boards and the investigators is a triad at the local level for ensuring compliance and reporting is recapitulated throughout the beginning of the NIH Guidelines in Sections 1, 2, 3, and 4, and I would be happy to supply you with the exact citations. And again, as I just mentioned, each and every time an investigator submits a protocol, we remind them in no uncertain terms of their obligation to report.

Senator FRIST. So you are doing everything right, and the researchers out there are not complying, and you are basically saying you have done your job in telling them what the requirements are, so the breakdown is with them?

Dr. PATTERSON. I think that investigators have violated the Federal guidelines. That is not to say that we will not redouble our efforts and take every additional measure——

Senator FRIST. If I talk to these 200 investigators, if I just called them on the telephone right now, they each know that they need to report every adverse event to you, number one, and number two, they have not been doing it?

Dr. PATTERSON. They should know that.

Senator FRIST. Now, just for perspective, we had these 200 trials—how many of the trials involved using an adenovirus? Fifty percent? One hundred percent?

Dr. PATTERSON. About 93.

Senator FRIST. So roughly half of the 200 trials? We had these 691 reports on the use of the adenovirus, based on what you have told me. What about the other 100 trials out there—are we going to hear about their adverse events later?

Dr. PATTERSON. The other trials—let me correct you—93 of the 372 trials that NIH has, so adenovirus vectors account for about 25 to 30 percent of all current trials.

Senator FRIST. All right.

Dr. PATTERSON. In 1999, NIH received approximately 100 reports of serious adverse events, approximately 70 of which were on other types of trials. The NIH and the RAC have consistently looked at the serious adverse events reported and discussed them at RAC meetings and have made this data available to the public and carefully monitored what is going on with the other types of vectors that are used.

Senator FRIST. Again let me go back. We have 300 trials, about 25 percent adenovirus, and just in the last few months, we learned of over 600 adverse events that we did not know anything about. What about the other 75 percent of the trials in gene therapy that we have not heard about—we have not heard about—can we expect as a public or as a Congress to hear an unloading of a number of adverse events there that we have not been notified about?

Dr. PATTERSON. Well, again, I think that we are taking every step we can. We have contacted directly all institutions conducting this research to ask them to report to us any heretofore unreported serious adverse events.

Senator FRIST. And based on your past experience in the last several months, they have not been reporting to you. You sent a letter out, 600 all of a sudden report, and now we have 75 percent more experiments—you have sent a letter out to them as well?

Dr. PATTERSON. Yes.

Senator FRIST. But the letter that you sent out in October was just adenovirus?

Dr. PATTERSON. That is correct. In November, we——

Senator FRIST. You sent another letter out to the rest of the trials?

Dr. PATTERSON. Yes, sir.

Senator FRIST. Have you heard from them?

Dr. PATTERSON. We have had a number of adverse events reported in response to that letter as well.

Senator FRIST. Has that been reported either in the media or to us, in terms of the numbers there?

Dr. PATTERSON. I can tell you directly now—I said we got 100 reports in 1999. We received reports after the November letter of approximately 40 adverse events.

Senator FRIST. Were there any deaths in that group?

Dr. PATTERSON. There were deaths that were reported that were attributed to the progression of underlying disease or concomitant medications. There was none that was attributed directly to the gene transfer.

Senator FRIST. OK. Again, this report just goes right to the heart of the trust, from the physician investigator to the patients to the researchers, and we have just got to lock this down.

Let me switch quickly, Dr. Patterson, to RAC. The Recombinant DNA Advisory Committee is to conduct public review and discussion of the scientific and the safety and the ethical issues in human gene transfer research, as you said, particularly in the field of novel gene transfer studies. This role has changed over the years—most people are not aware of it, I think, across the country—but it has changed in recent years as the RAC's approval authority for gene therapy trials was removed by a decision made at the NIH in 1996. I think this is very important for us to address.

Does the NIH believe that the removal of this authority—this approval authority—at the NIH led the research community to believe that for some reason, they do not need to report these adverse events as they have in the past?

Dr. PATTERSON. Well, this is a question that we have been asking ourselves, and as we have been discussing here this morning at length, we believe that the guidelines and our letter sent to inves-

tigators are quite clear. It is obvious that there has been widespread noncompliance with the NIH Guidelines' reporting requirements, and that is unacceptable. The NIH Director has formed a special advisory group that is looking at the role of NIH oversight in this field of research and has specifically asked this group to address the very question that you have asked, sir—what options need to be considered, including a possible return to RAC's approval authority.

Senator FRIST. With the removal of that authority in 1996 for RAC to approve the gene transfer trials, was there a documented decrease in the amount of reporting of adverse reactions? I know it is a tough question, but we had a radical change in policy in 1996 which removed approval authority; we have a huge problem with reporting of adverse reactions now. Was it a problem before when they had that authority?

Dr. PATTERSON. Right, and again, we have asked ourselves this same question. Let me also just for the record State that RAC relinquished approval authority on October 31, 1997. But in collaboration with FDA, we are conducting a comparative analysis of the numbers of adverse events reported to NIH and FDA, as Dr. Siegel has already mentioned, and that analysis is focusing both on the time period prior to the relinquishment of RAC approval and to the period after RAC approval was relinquished, so we can try to get at the question you have just asked.

The preliminary analysis that we have done of 34 INDs does not indicate a dramatic change, but I think that there are sampling errors, and which protocols you pick has a lot to bear on that question, and I think the analysis——

Senator FRIST. I think that from an investigator's standpoint, when you have Government asking you for things, saying it is important, and we control your approval, and then, all of a sudden, they say we are not in that business anymore—maybe the investigator will say, Well, we do not need to report these things, they are not conducting the approval anymore. So I think it is worth looking at, and I understand you are addressing it, and we would encourage you to do so.

Mr. Chairman.

Senator Jeffords. Dr. Siegel, you listed "enhancing regulatory research" as one of the FDA's steps to ensure greater patient safety. Could you elaborate on that point? What are you going to do?

Dr. SIEGEL. Yes. I think there are two different ways in which our regulatory research has been critical in the regulation of gene therapy. One is that we have research programs that specifically look at the safety of gene therapy vectors or the adequacy of different, new experimental methodologies to test for problems in a vector preparation, for example.

The science in this field is moving along, as you know, extremely rapidly, and new approaches are developing practically on a daily basis, and they each raise new questions. Often, by the time you can validate certain types of testing or certain types of vectors, there is something better to do.

But the research also plays another critical role in this picture, which is that because of the way that the technology moves, it is critically important that the FDA have scientists who are at the

forefront of their field, who are at the State of the art, who understand what is being done, who can recognize problems, deficiencies, better ways to do it and so forth. And I think our research program, in addition to addressing safety issues, also plays an important role in the recruitment and retention of qualified and leading scientists in this area.

Senator Jeffords. You listed increasing oversight of gene therapy INDs as one of FDA's steps to ensure greater patient safety. In what way would you increase the oversight?

Dr. SIEGEL. I think that was specifically a reference to increasing inspectional oversight of gene therapy INDs. We intend to do more inspections on gene therapy INDs to determine if some of the types of problems we have seen are isolated, if they are more widespread, to ensure that problems that exist are corrected, problems of the sort that we have discussed that are in the Form 483.

Senator Jeffords. Dr. Frist.

Senator FRIST. Thank you.

Earlier this morning, we talked about informed consent, and I want to at least broach it, and we can discuss it further as we go forward trying to fix the identified problems. So I have a question for you both.

We have to look at informed consent, we have to look at confidentiality, and we have to look at safety—three issues that really strike at the heart, I believe, of that informed consent progress. And again for my colleagues, the informed consent process is really where you lay out to the patient, the nature of the protocol, the risks, the inherent advantages, the State of the art, the promise for the future. And although it is written on a piece of paper, the reality of it is that you do go through the piece of paper, but there can be real bias in that room, there can be things emphasized and deemphasized in what is written on paper. So what is written on paper is critically important, but the nature in which it is presented is critical as well—in a room with patients typically, or often, with incurable diseases, and investigators—some of whom have vested interest, professional vested interest, to see that this thing works—some even see the Nobel Prize out there when they are presenting it to that patient. Some have financial interests. These are issues that ultimately, we have got to address in the year 2000 because we have not addressed them, really, in a decade or two decades. We cannot do all of that now, but let me ask a very direct question to each of you about informed consent.

Do the institutional review boards at different facilities consult with the NIH and the FDA on developing the informed consent forms and explaining the potential benefits and risks to human subjects, and is that process working from the standpoint of the NIH and the FDA?

Dr. Siegel.

Dr. SIEGEL. Well, from an FDA perspective, I can say that we only on occasion get a direct contact from an institutional review board to our reviewers, and that will often happen in the context of a very new therapy where a chair of a board will call up and say, "We have some concerns. We may not have the appropriate expertise, and we have some questions. Is there FDA guidance about that, and what is the FDA doing?"

The IRBs will frequently make their approvals—they will remind the sponsor, and they give the approval contingent on FDA review and conversely, FDA approval is always contingent on IRB approvals.

But the other critical piece of that interaction is that the FDA does recognize that not every IRB has the information about gene therapy as it is happening across the country or the types of expertise or the full range of expertise that might be useful. And we do review the initial proposed written informed consent form for every gene therapy trial, and we can, and very frequently—I cannot give you numbers—but very frequently do, including in the case, for example, of the University of Pennsylvania OTCD trial, instruct and require that additional information be included in the informed consent form.

Senator FRIST. Dr. Patterson.

Dr. PATTERSON. The informed consent of patient is an absolutely critical component of clinical research, and the RAC has a longstanding history of carefully evaluating not simply the informed consent document, but the entire process by which patients are informed, notified of the existence of a protocol, talked to about their potential participation, how risks are presented to them. And these recommendations on specific protocols have always been forwarded from the RAC to the local IRBs for their consideration as they are facing looking at these protocols on their desks on a day-to-day basis.

Senator FRIST. So both of you are entirely pleased, satisfied, with each of your agencies in terms of protocol for informed consent and your contact with institutional review boards?

Dr. SIEGEL. That is a very broad statement. As you have acknowledged, informed consent is a very complex process. A great deal of it—the most critical part of it is in the one-on-one interaction, as you know and as you have pointed out, and of course, we are not there at that time.

What our agency does for gene therapy, in addition to reviewing all the additional informed consent protocols, is have inspectional activities where it looks at the adequate documentation—are the forms there, are the forms signed, or whatever. Those are the issues specific to how we review gene therapy protocol.l

But I want to say that this is, as you have acknowledged, a very big issue, a much bigger issue than here, and I am not sure that I am in a position to say that our agency is satisfied with everything that is done regarding informed consent.

Senator FRIST. Dr. Patterson?

Dr. PATTERSON. I think that because the informed consent process is at the heart of matters, as you have said, we can never be satisfied with the process. We have heard this morning some very good suggestions on how the process could be improved. I think that the NIH has in the past and is committed to continuing and redoubling our efforts to communicate on the local level and to participate in meetings with IRBs.

So while I think we have a good process in place, I think there is room for improvement.

Senator FRIST. When was the last time the Federal human subjects regulations were upgraded with respect to the guidelines for informed consent? Do you know?

Dr. PATTERSON. I do not know that, but I would be happy to get that information for you.

Dr. SIEGEL. We do not know that.

Senator FRIST. Again, we cannot go all the way through that, but again, as you have said, it is at the heart—this whole trust relationship starts right there, I believe, in that room where consent is given, and we need to continue to ask ourselves how we can improve that process at the Federal level so it will filter down to that room.

One last thing—and I apologize for going on for so long, and we will go to the third panel right after this—one issue with the NIH Guidelines. As you said, the NIH is undergoing review of the Guidelines with respect to reporting requirements for gene therapy trials. The amendments to the Guidelines were released on November 22, 1999 for public comment and were discussed at the December meeting of the RAC.

The plan involved adding language to the NIH Guidelines that would require—and let me just read the two sentences—"that serious adverse event reports must not contain any trade secrets or commercial or financial information that is privileged or confidential and that all information submitted in accordance with the NIH Guidelines will be considered public unless NIH determines there are exceptional circumstances."

Patient groups have come forward; industry has come forward and raised concerns regarding this language. Industry is concerned that information released by the NIH would still contain some proprietary information which would in some ways set them back from a competitive standpoint. Patients are concerned that the information released will contain—and you addressed this in part—personal identification—the privacy of patient information is their concern.

Could you summarize for the members of the committee the comments of RAC at the December meeting, or how it has progressed since that time in terms of this specific reporting requirement?

Dr. PATTERSON. Yes. There is a working group of the RAC that is specifically charged with undertaking the revision of that proposal in light of the public comments that were received.

The position of the RAC to date has been that adverse event reports belong in the public domain so they can inform other investigators, they can inform prospective patients. The RAC has held to that principle.

It is a complex issue because some of the manufacturing details, issues of patentable information about how a product—some specific detail of manufacturing—perhaps need not be included in an adverse event, and there is no interest on the part of NIH to include such information if it has no bearing on the adverse event and is an accurate interpretation.

Regarding the second point, patient confidentiality is a critical issue as well, and while it is important that the information be out there, it is important that it not contain information that could identify specific individuals.

I think those two principles, the RAC has endorsed. I think that what is at issue and what the group is trying to balance is the universe of adverse events that are reported—do we report every, single adverse event immediately, or do we report serious, potentially, possibly related to the intervention, immediately—and then all others in an annual report.

I think that is the part of the puzzle that the RAC is grappling with now, and at the upcoming meeting in March, they will present on their deliberations and in conjunction with the advisory committee to the NIH Director, they will be preparing a final recommendation on how NIH will receive, analyze, and publicly disclose this critical information.

Senator FRIST. I think it is an important component which again we do not have time to address. Most of the time today is spent on getting the information up to our agencies, having it appropriately used, and then, the flip side of the question is how we get it back down, how we report it, how we disseminate it. And we are not going to have time to address all of that today, but it is a huge issue that was brought up by Mr. Gelsinger early on in terms of how it can be shared and one that, again, I want to continue to keep a real focus on.

You say NIH says make these adverse events public; FDA says make them public, or keep them private?

Dr. SIEGEL. Well, by law and regulation, our policy approach to date has been that adverse event information submitted to us is not available to the public. Now, I should note that that does not mean that that information is not shared with other investigators as appropriate to protect the safety of patients. So if we get a specific report that has bearing on patients in the trials, what we will do is go to the sponsor who submitted the report and say we believe it is important that we make this information available to other sponsors, and in my experience, the answer is always yes.

But we do not broadly disseminate that information. We do, however, recognize certain values and interests in increased public disclosure of these protocols, and as I have indicated and indicated in the testimony, we are planning to issue a proposal that would, within the scope of our governing laws, permit an increase of information that we think would be beneficial to the public health to release.

Senator FRIST. Does the FDA feel that its hands are tied in its ability to more publicly report adverse conditions?

Dr. SIEGEL. The law limits the extent to which we can do that. There is some thinking in the agency that we can look at the laws differently and rewrite rules that would allow more disclosure, and I think the next few months or the next time period will tell more about whether in fact we can or cannot do that.

Senator FRIST. But that would require a change in the law, not in just the regulations?

Dr. SIEGEL. Well, the law provides the limit in terms of both trade secret, commercial, confidential, and personal information that we cannot—as I was saying, we believe that within the law, there is more that we can disclose in the area of gene therapy, and we are looking at how to do that.

Senator FRIST. OK. Thank you both very much. Again, I apologize for both the length of the time and the nature of the discussion, but as both of you realize, it is tremendously complex, it is one of the more important issues that I think our society has to address from a Government standpoint. So I appreciate both of your participation. We look at this as a real foundation for further discussions as we go forward.

Thank you very much.

Senator FRIST. I will ask the third panel to come forward, please.

I am excited about the third panel today, and I apologize for the length of time it has taken to get to the panel. I think the third panel really brings together the excitement of the science and the promising future of gene therapy, with a discussion of the bio-ethical issues that are introduced by this new science, and the competing interests of the various stakeholders in this type of biomedical research.

We have with us three individuals, experts in their field.

Dr. Inder Verma is a professor of molecular biology at the Salk Institute in La Jolla, CA. Dr. Verma, the president-elect of the American Society for Gene Therapy, will explain the rationale and science behind gene therapy as well as its potential uses and limitations. He received a master's degree in biochemistry in India; a Ph.D. in biochemistry in Israel; he did his postdoctoral training at MIT.

Dr. LeRoy Walters is the director of the Kennedy Institute of Ethics at Georgetown University, where he also serves as a professor in the Department of Philosophy. As a former chairman of the Human Gene Therapy Subcommittee of the Recombinant DNA Advisory Committee, Dr. Walters will explore the critical bioethical issues involved in patient participation in experimental clinical trials, including informed consent and conflicts of interest. Dr. Walters received his Ph.D from Yale.

Ms. H. Stewart Parker of Seattle, WA is president and CEO of Targeted Genetics Corporation. Ms. Parker is the former chair of the board of the Washington State Biotechnology Association and currently serves on the board of the Biotechnology Industry Organization on whose behalf she is testifying today. Ms. Parker will present the views of the biotech industry regarding current and proposed NIH and FDA guidelines. She received her M.B.A. in finance and international business from the University of Washington.

I appreciate all of you being here today and appreciate your patience. This is a tremendously exciting panel that will discuss the breadth of issues involved in gene therapy research.

Dr. Verma?

STATEMENTS OF INDER VERMA, PROFESSOR OF MOLECULAR BIOLOGY, LABORATORY OF GENETICS, THE SALK INSTITUTE, LA JOLLA, CA; LEROY WALTERS, DIRECTOR, KENNEDY INSTITUTE OF ETHICS, GEORGETOWN UNIVERSITY, WASHINGTON, DC; AND H. STEWART PARKER, PRESIDENT AND CEO, TARGETED GENETICS CORPORATION, SEATTLE, WA, ON BEHALF OF THE BIOTECHNOLOGY INDUSTRY ORGANIZATION

Mr. VERMA. Thank you, Senator. I am both honored and pleased to testify before this subcommittee to explain to you the science of gene therapy, its potential benefits to society and safety issues related to its practice in patients.

Gene therapy is a form of molecular medicine which will have major impact on human health in the coming century. The basic concept of gene therapy is simple: Introduce the gene, w hose product should have the ability to either cure the disease, ameliorate the disease, or perhaps slow down the progression of the disease.

The scope of gene therapy has considerably broadened in the last decade. Not only can we now consider the correction of genetic defects, of which there are thousands, and with the Human Genome Project completed, we will learn more about them; not only can it actually help in curing many cancers by completely destroying and killing them, but it has influence in cardiovascular disease, in a number of neurological diseases, and perhaps even in elimination of many pathogens.

Rarely has there been a technology in human health which can have such a pervasive effect on human health in the coming century. This is why there is excitement. This is why so many people are devoted to research in gene therapy, because its potential is enormous. The public is excited, the patients are excited, and scientists are excited because this offers an opportunity to bring their work into clinical practice.

The key to success of gene therapy really lies in how to deliver the genes. It is not the concept—it is how you deliver the genes. There are a number of ways to do so. Some people introduce the gene directly by DNA direct injections, which is safe, but unfortunately not as efficacious as you might want to see it. In the majority of the 375 trials, 80 percent of them have been using viral vectors. By viral vectors, we mean viruses which have the ability normally to cause a disease, but one can debilitate them by removing the disease-causing potential and substituting them with a therapeutic gene, so the viral is fooled into behaving like a virus, but in fact is now carrying the therapeutic rather than the pathogenic gene which it normally carries with it.

There have been three principal kinds of vectors—retroviral vectors, which normally cause cancer in animals—not in human that we know of, but in animals. They are wonderful tools because they can introduce genes that have long-term expression. Unfortunately, they cannot introduce genes into nondividing cells, which means that we cannot put them in the brain, liver or lung, which are normally nondividing.

A second kind of vector about which we have heard a lot today is the adenoviral vector, which is the common cold virus. The nice thing about this virus is that you can make trillions of virus par-

ticles, so you can make a lot of it. Unfortunately, it has side effects of a) making short-term production of the protein, which is why Jesse Gelsinger was told it could not produce protein for more than 14 or 15 days; furthermore, it has serious immunological consequences because at high doses, the virus is toxic and has liver toxicity. Nevertheless, this virus has been used much more in the case of cancer, where the cells needed to be killed anyway, so the toxicity is less of a concern.

The third vector is an AAV vector, which is a relatively new one, and that is now being considered as a very interesting vector for which trials are being conducted.

Another vector which I am personally interested in is the vector based on the AIDS virus. We have been able to debilitate the AIDS virus to introduce genes, and now they are able to introduce genes directly into a wide variety of cells which are both dividing and nondividing. Again, there was a policy conference discussion of this; more is being done; safety vectors are being made. Nevertheless, it is a very exciting venue for introducing genes.

If the concept of gene therapy is so simply, the critics have often asked, why has it not been more successful? Why are there not resounding successes with gene therapy?

The field of gene therapy is young, as you mentioned in your introduction, Senator. It has only been 10 years since the first ADA patients were trialed. It was accompanied by enormous excitement, but unfortunately, a lot of hype and unrealistic expectations. We have now learned that these vectors are not so easy. They do not make the protein as long as we wish them to make it, the immunological consequences are unforeseen, and we are learning about them.

The interesting point to mention here is that there has been tremendous progress over the last many years. Better vectors are coming. Long-term production of the protein is being made. And just to add to that, there was a marvelous talk at a recent meeting of gene therapy where two patients treated with a rare immunodeficiency much like ADA in Paris have now shown complete cure for 1 year. This is fantastic promise for gene therapy. These children will live long lives. There are anecdotal examples for hemophiliacs. There are anecdotal examples for cancer. The reason I say they are all anecdotal is because until they are published in peer-reviewed journals, one really cannot comment, because all we can tell you is what we have learned at meetings when people give talks. That is really very exciting.

The field of gene therapy has also undergone an enormous amount of scrutiny both from NIH and from the public. There were special reports at NIH asking the question, is gene therapy efficacious, and suggestions were made, and people were asked to actually work more on basic sciences at that time and not so much on the clinical sciences, because that work was required for its success.

Patient safety in clinical research is always of paramount concern. It is true that new modalities pose risks, both known and unknown, but that is all the more reason for us to be even more vigilant than in any other technology, because we do not know what this might do.

There are ways, as you have heard—RAC, FDA, IRC, IRBs—there are many, many ways in which gene therapy is being controlled.

After saying all that, one would like to know: If all that was in place, what failed the brave Jesse? How did we fail brave Jesse that it did not work?

You have heard many suggestions today, and I am actually quite encourage to see how a close harmony between FDA and RAC will allow perhaps better monitoring, and we are hoping—this is a young science. We are just beginning to get the fruits of this science. Tragic incidences like the unexpected death of Jesse Gelsinger make us pause. We think back about what we could have done differently, what we can do differently next time, and that is what this meeting is about, to help us.

I was deeply saddened to hear from Mr. Gelsinger the sad comment of a colleague who called Jesse's death "a pothole in the road to gene therapy." That is not how we see it. We feel terrible about it, and we are very sad. This is how our community feels. This is a very serious event, and we take it very seriously.

But at the same time, we believe we have to move forward. We have to learn from this technology, and what we would like to do is be able to do a better job, learn more from this, and move this field to what I would consider a major challenge and a major benefit into human disease as we go through the next century.

Thank you very much for inviting me. I would be happy to answer questions.

Senator FRIST. Thank you, Dr. Verma.

[The prepared statement of Mr. Verma follows:]

PREPARED STATEMENT OF INDER M. VERMA

Mr. Chairman and members of the Committee: I am Inder M. Verma, American Cancer Society Professor of Molecular Biology and Director of the Laboratory of Genetics at The Salk Institute in La Jolla, California. I am also an Adjunct Professor in the Department of Biology at the University of California, San Diego and the President-Elect of the American Society of Gene Therapy. I am honored and pleased to testify before the Subcommittee and explain the science of gene therapy, its potential benefits to society and safety issues related to its practice in patients.

Gene therapy is a form of molecular medicine which has the potential to influence vast areas of human health in this century. The basic concept of gene therapy is simple—introduce a gene whose product has the ability to either cure or slow down the progression of disease. Its broad scope encompasses, correction of genetic defects, killing cancer cells, preventing cardiovascular disease, interfere with the progression of neurological disorders and eliminate infectious pathogens. Rarely in the field of human health a technology has held this much promise and therefore it has captured the imagination of so many scientists and raised the hopes of potential beneficiaries and the public at large.

The key to success of gene therapy is the development of methodology for efficient delivery of genes to the desired target. Generally two types of approaches have been used (i) introduction of genes by physical methods which include direct injection of genes (DNA), either by itself or in various lipid formulations; and (ii) manipulation of disarmed viruses as vehicles to ferry genes. Of the nearly 375 current gene therapy trials, over 75–80 percent involve the use of viral vectors. The physical methods of introduction of genes offer safety advantages, but are less efficient in providing long term production of the desired gene product. The principle behind producing recombinant viruses carrying therapeutic genes (viral vectors) is to either debilitate or eliminate the disease causing entity of the virus and substitute it with the therapeutic gene. The advantage of the viral vectors is their ability to transfer genes to large numbers of cells for sustained periods of time, in some cases the entire life of an experimental laboratory animal. Presently there are three major viral delivery systems used in clinical trials: (a) Retroviral vectors: These delivery vehicles are

based on viruses which in their native state can cause cancer in mice. In the last decade-and-a-half, scientists have been able to engineer retroviruses to contain therapeutic genes and eliminate any disease causing potential. Nearly half of all clinical trials involving well over 3,000 patients have used retroviral vectors. To date there have been no reported adverse events ascribed to recombinant retroviral vectors. While the retrovirus based delivery vehicles can result in long term production of the desired gene product, they have however a major limitation-they cannot introduce genes into non-dividing cells. Thus, cells of a desired tissue have to be taken out, grown in dishes, exposed to retroviral vectors, and then transplanted back into the patient. Not only is this process cumbersome, many tissues like brain, lung, and heart are not amenable to this approach. (b) Adenoviral vectors: The common cold viruses have been adapted to contain therapeutic genes and offer two major advantages (i) up to 10-100 trillion virus particles can be conveniently and reproducibly generated, and (ii) they can introduce genes in both dividing and non-dividing cells and therefore overcome a major limitation of retroviral vectors. One of the major problems of adenoviral vectors is the relatively short duration (ranging from a few days to weeks) of the production of the therapeutic gene product due to immunological rejection of cells harboring the vector. New improved adenoviral vectors with less immunological impediments are being generated but all adenoviral vectors used in clinical trials to date have relied on the first or second generation of adenoviral vectors which still manifest undesirable immunological consequences. Additionally, very high doses of recombinant adenoviruses have severe adverse side effects like liver toxicity, high fever, or disseminated intravascular coagulation. The use of adenoviral vectors constitute only one-fourth of all clinical trials—the vast majority of which are for cancer related diseases through intraturnoral delivery. (c) Adeno-associated vectors (AAV): These novel vectors are based on non-pathogenic viruses which require adenoviruses for their propagation. Scientists have engineered recombinant AAV-vectors which do not require infectious adenoviruses for production and therefore are free of the complications associated with adenoviruses. Presently they constitute less than 5 percent of all clinical trials, but their long term success in experimental animal model systems bode well for their future clinical applications.

Finally there are other novel vectors on the horizon which have not yet entered clinical trials. One of these is based on the use of lentiviruses, which are a group of retroviruses and harbor the AIDS virus as one of its members. Safe lentiviral vectors are being generated where the disease causing entity of the virus has been completely eliminated. My own work is intimately associated with the development of lentiviral based vectors, which have the unique advantage of introducing genes into dividing and non-dividing cells. Other novel vectors include the use of neuron specific Herpes viruses, non-pathogenic cytoplasmic Sindbis viruses, etc. The important point I wish to make is that there are no perfect delivery systems, each has its advantages and limitations. The choice of the vector is dictated by the nature of the disease. If the production of foreign protein is required for sustained periods, then one would have to use retroviral/lentiviral or adeno-associated viral vectors, but if the purpose is to kill the ungainly cancer cell or produce a therapeutic protein for a short time, then adenoviral vectors are ideal. It is therefore not surprising that a substantial effort in the field of gene therapy is still devoted to generating delivery vehicles which are safe and efficacious.

If the concept of gene therapy is so simple, and promise so great, the critics have often asked, where are the successes? The field of gene therapy is only 15 years old, and the first patient was enrolled less than a decade ago. The first ADA (adenosine deaminase deficiency) and the cancer trials in early 1990's at the NIH were greeted with great anticipation. The excitement was genuine, but regretfully, was accompanied by great hype and unrealistic expectations. There were unexpected hurdles, the extent and the duration of the foreign protein was much less and shorter than expected, and the immunological consequences unforeseen. Did we start too soon? Should we have done more animal model studies? Was there adequate preclinical data? Although we can debate the merits of these issues ad infinitum, the fact of the matter is that great strides have been made in the last decade in overcoming some of the hurdles, sharpening the focus on safety, generating better delivery vehicles, developing new approaches to combat unexpected immunological consequences, and acquiring a more realistic appreciation of the clinical end-points. The field of gene therapy has always undergone extensive public scrutiny and NIH review, as exemplified by the Orkin-Motoulsky report to the NIH Director in 1996. We are finally beginning to witness some limited successes. Just three weeks ago at a gene therapy meeting in Keystone, Colorado, Dr. Alan Fischer from Paris described the complete cure of two young children suffering from a rare form of immunodeficiency. Although this work has not yet been published in a peer-reviewed journal, it ap-

pears that these two children (and at least two additional ones) are producing the deficient protein for nearly a year without any sign of decline. These kids will live a normal life—that is the fantastic promise that gene therapy holds. We also heard some preliminary good news on the gene therapy trials of two hemophilic patients. There are also many tantalizing anecdotes of success in cancer gene therapy. I should once again emphasize that over 90 percent of all clinical trials are presently designed for safety or phase I studies. There are to my knowledge only three phase III studies of clinical efficacy, all in the area of cancer, where the disease is often terminal.

The patient safety in clinical research is always of paramount concern. It is true that new modalities of medicine pose risks, some expected and some unexpected, which calls for even greater vigilance. The Recombinant DNA Advisory Committee (RAC), Food and Drug Administration (FDA), and the Office of Biotechnology Activities (OBA) are all involved in monitoring safety of patients in gene therapy related clinical trials. The RAC holds its meetings in an open public format and discusses the potential safety and efficacy issues publicly. The investigators have to provide proof of safety of their vectors, preclinical efficacy and toxicity data on animals, and answer questions related to not only scientific issues, but also patient consent forms and other ethical issues. I have served as a RAC member and can testify to the diligence and seriousness with which its members undertake their task. The RAC can make recommendations to the advisability of a clinical protocol, but it is the FDA, the regulatory body, which must give the final approval for gene therapy IND's (investigational new drug) before patients can be enrolled in the trial.

Much has been made recently of the loss of RAC's authority in the period between 1996–97. At the request of Dr. Harold Varmus, NIH Director, I was asked to chair an Ad hoc committee (RAC overview committee) to review the function of RAC in approving gene therapy clinical trials. Our committee recommended to the Director that RAC serves an extremely important function to keep the general public informed and involved in gene therapy related activities of the NIH. We proposed that RAC assumes the responsibilities of being a policy forming body rather than a regulatory body as that authority lies with the FDA. We felt that duplication of the regulatory process in two federal agencies was not optimal, but was essential to discuss gene therapy related issues in public because deliberations of the FDA with investigators are confidential. We further recommended that the RAC and the FDA have a close working relationship and harmonize their requirements from the investigators. There are clear cut guidelines on reporting adverse events to the RAC.

The question that is on everyone's mind is that if all the procedures were in place, how did the unfortunate events leading to the death of brave Jesse Gelsinger occur? There have been extensive discussions of the possible causes that might have lead to the death of Jesse. I cochaired the RAC committee to review the adverse effects of adenoviral gene therapy clinical trials. No single cause has yet emerged, but the general consensus is that the death of Jesse was likely due to the toxicity of the adenoviral vector. While it is true that the scientific community was aware of the toxicity associated with presently available adenoviral vectors, to date only one death among 1,100 patients treated with adenoviral vectors can be directly linked to the vector, and hence the gene therapy protocol. The committee is presently formulating its recommendations to the NIH Director.

Before a clinical protocol is approved for filing of an IND, it has to go through the Institute Review Board (IRB), Institute Biosafety Committee (IBC), RAC, and finally the FDA. At each step there are clear cut rules and guidelines to which the investigator must adhere before approval can be granted. There are also penalties if the investigators do not conform to the approved practices. In clinical trial using ornithine transcarbamylase (OTC) gene in second generation adenoviral vectors at the University of Pennsylvania, the FDA has recently identified a number of procedural lapses and irregularities. It is my strong belief that if violations have occurred, the responsible parties should face the consequences. I have not yet seen the response from the investigators from Univ. Penn., therefore I have to withhold my judgement. To restore the public's confidence in clinical research and in a federal regulatory agency like the FDA, charged with patient safety and protection, it is essential that any violation of approved procedures be dealt with swiftly and appropriately. Society has a huge stake in science and scientists will be well served to remind themselves that the public's confidence and trust is essential for the continuity of their scientific endeavors.

Mr. Chairman, gene therapy offers an unprecedented modality of medicine with enormous potential. It is a young science which is just beginning to show the fruits of its labor. We still have a long way to go. Tragic incidences like the unexpected death of Jesse Gelsinger give a reason to pause and take stock of the progress and pitfalls of the technology. We must learn from our mistakes, but continue to move

forward to harvest the untapped potential of this novel technology to reduce the burden of human disease. I thank you, Mr. Chairman, for giving me the opportunity to speak to you on gene therapy. I will be very happy to answer any questions that you may have.

Senator FRIST. Dr. Walters.

Mr. WALTERS. Mr. Chairman, thank you for inviting me to discuss ethical issues in gene therapy research.

In my written statement, I review the 25-year history of the Recombinant DNA Advisory Committee. Back in 1990, the Committee had the privilege of reviewing and approving the first two gene therapy studies. And in September of that year, Ashanti DeSilva received gene therapy at NIH in the first clinical study undertaken after that approval.

We had so much hope in those days that this field would be successful, and soon, with many diseases. By the mid-1990's, we began to see that the situation would not be quite so simple and that success would not come quite so soon.

One of the best moments in the entire history of the Recombinant DNA Advisory Committee in my view occurred in June of 1995. At that meeting and after 6 months of intensive work by the staff, RAC members presented a comprehensive overview of the field of gene therapy to date. That overview detailed adverse events as well as the minimal success to date.

The results of that overview were published in 1996 in the journal Human Gene Therapy, and I would like to ask that a copy of that overview be included in the record.

Senator FRIST. Without objection, it will be made a part of the record.

[The document referred to follows:]

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Mary Ann Liebert, Inc.

Special Feature

Gene Therapy in the United States: A Five-Year Status Report

GAIL ROSS,[1] ROBERT ERICKSON,[2] DEBRA KNORR,[3] ARNO G. MOTULSKY,[4] ROBERTSON PARKMAN,[5] JUDE SAMULSKI,[6] STEPHEN E. STRAUS,[7] and BRIAN R. SMITH[8,9]

INTRODUCTION

HUMAN GENE TRANSFER has been heralded for its potential to revolutionize modern medicine through the use of recombinant DNA technology to treat inherited and acquired diseases. Over 5 years have now passed since the first human subject underwent gene transfer for the treatment of severe combined immunodeficiency. At its June 1995 meeting, the National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) Data Management Subcommittee reviewed the preliminary results of all 107 human gene transfer clinical trials involving 597 subjects in the United States. While it is apparent from those data that human gene transfer research is progressing at a remarkable rate, statistically significant information regarding long-term efficacy and adverse consequences are still generally lacking. In addition, while the majority of protocols approved by the NIH are for the treatment of subjects with limited life expectancies (*e.g.*, patients with advanced cancer and HIV infection), the long-term consequences of gene transfer technology will ultimately only be demonstrated in subjects with better long-term prognoses. Nonetheless, the preliminary results reported to the RAC represent a state-of-the-art summary of both the potential and the current reality of human gene transfer treatment.

The RAC was established in 1974 as a committee of scientists, physicians, ethicists, lawyers, and consumer representatives whose charge has been to advise the Director of the NIH on all matters concerning recombinant DNA research and whose deliberations have been held in a public forum. All human gene transfer experiments proposed by investigators at federally funded institutions have been reviewed by the RAC and subsequently submitted to the NIH Director for approval or disapproval. This public review has occurred in addition to the traditional "closed door" review of investigational therapies by the Food and Drug Administration (FDA).*

The RAC had requested that the principal investigator of each of the 106 RAC-approved studies submit a progress report at 6-month intervals that included both preliminary and published results of the investigation. Although there was no regulatory requirement for investigators at nonfederally funded institutions to submit information to the RAC, one company submitted such information for their FDA approved trial, bringing the total number of protocols reviewed to 107. The authors believe that with the inclusion of this voluntary data submission, nearly all experimental protocols involving human gene transfer carried out in the United States through June, 1995 are included in the current summary. The present information is based on those Progress Reports (RAC, 1995).

OVERVIEW

At the time of the report, 94 of the 106 protocols receiving favorable RAC review had been approved by the NIH Director, with 12 awaiting NIH approval, pending submission of further information requested by the RAC. One protocol favorably reviewed by the RAC was disapproved by the NIH Director, and one single patient protocol, not recommended for approval, was ultimately permitted to proceed by the Director. Seventy-eight of the protocols were also approved by the FDA. Nineteen studies were closed because they had completed recruitment of patients; three studies were approved by the NIH but were never

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[9]All authors (except D.K.) were external members of the NIH Recombinant DNA Advisory Committee (RAC).

*In May, 1996 the Director of the National Institutes of Health announced his intention to abolish the RAC. It is expected that reviews of all future human gene transfer protocols will be made solely by the FDA and that the Office of Recombinant DNA Activities will publish an annual report of all approved protocols in which investigators are affiliated with federally funded institutions.

initiated; 55 were ongoing; and 14 were approved by the NIH and FDA but had not yet enrolled patients.

As of June, 1995, 597 subjects in the United States had received experimental genetic material. This represents over 85% of the total patients worldwide who have received gene therapy (Marcel *et al.*, 1995). Figure 1 illustrates the rate of increase in the cumulative number of protocols approved over the past 5 years. Although gene transfer studies were initiated in 1989, it was not until 1991 that there were multiple new projects approved in a single year. The total number of patients who underwent gene transfer is not evenly distributed among protocols. Two protocols (both involving HIV vaccination and both sponsored by Viagene, Inc.) account for 168 of the patients entered whereas all other protocols had entered 45 or fewer patients each. About 35, or 6%, of the patients have been children under 18 years of age.

One hundred three (97%) of the studies are classified as Phase I (evaluation of safety), two, as Phase I/II, and only one (gene therapy for HIV) approved in March, 1995, is considered a Phase II (preliminary evaluation of efficacy) study. There are no Phase III (evaluation of efficacy) studies of human gene transfer to date. Therefore, the explicit emphasis of the research so far has been on determining the safety of gene transfer procedures, sometimes with efficacy as a secondary goal.

One hundred thirty-four of the 597 enrolled patients have died since the inception of gene transfer studies. In the interest of maximizing the accrual of information on the anatomic distribution and persistence of transferred genes in treated patients, as well as potential unexpected toxicities, the RAC encourages all investigators to obtain autopsies specifically targeting these questions. The autopsy rate for those protocols for which complete information regarding post mortem examination was available is 21%, a number that compares favorably with figures reported from academic centers in general, but is below what one would hope for protocols in which the effort, expense, and interest is as great as in these studies.

Thirty-seven separate institutions in the United States are currently involved in human gene transfer trials. Most are academic institutions and the majority rely on outside sources for the vectors or gene delivery agents that are used in their protocols. A total of 34 vector suppliers have been identified, with 32% of protocols using vectors supplied by academic institutions and the rest (68%) using vectors supplied by industry. Most suppliers provide the vector for only a single protocol. However, the largest vector supplier, Genetic Therapy Incorporated, is responsible for the genetic material used in 39 (37%) of the protocols.

Apart from the cost of the vector itself, which is usually absorbed by the supplier, funding for gene transfer protocols comes primarily from the NIH. Approximately 55% of investigators reported at least partial NIH funding for their gene transfer studies, with the remainder receiving funds from both academic institutions and private foundations. Only 3–5% of protocols were funded solely by private industry, although the majority received partial industrial support including the cost of the vector.

One ongoing concern of academia, industry, and consumer advocacy groups has been the balance between adequate regulatory control of new technologies *versus* the speed at which potentially life-saving experimental therapies can be brought to the clinic. The Data Management Subcommittee of the RAC attempted to analyze some of the variables involved in the experimental phase of gene therapy with regard to that issue. Federal guidelines for Recombinant DNA Research Activities dictated that all protocols must first receive local Institutional Review Board (IRB) and Institutional Biosafety Committee (IBC) approval before being considered. Submissions to the FDA and RAC can be made simultaneously, but final FDA approval is contingent both on RAC and NIH Director approval. Although the data provided by the investigators are incomplete, sufficient information is available from 55–80 protocols to estimate the time from initial approval by the investigator's own IRB and IBC to RAC approval, from RAC approval to NIH Director approval, from RAC approval to FDA approval and from final approval of all agencies to entry of the first patient (Table 1). The median time between each stage of approval ranged from 3 months to 7 months. Thus, it often takes 1–2 years for a protocol to be completely approved from the time it passes the local IRB and IBC. It should be noted that the time to protocol approval has accelerated considerably in the past year due to a combination of increased experience on the part of investigators and regulators and development of accelerated and combined approval procedures by NIH and FDA.

GENE DELIVERY AGENTS

A major technical impediment to gene transfer is the lack of ideal gene delivery systems. Unless it is possible to deliver the gene to the appropriate blood or body cells and in sufficient quantities, gene therapy will not be efficacious. As outlined in Table 2, at least six approaches are currently in use in clinical trials, with retroviral vectors by far the most frequently used system. Of the six delivery systems available, over 85% of the protocols have relied on viral vectors. All of the viral vectors utilize approaches that involve complementation of defective vectors by genes inserted into 'helper' cell lines to generate the transducing infectious agent. This strategy inherently carries the potential risk of generating wild-type recombinants in the vector stocks. Although this risk exists, no evidence suggests that wild-type viral contamination has occurred in clinical trial material. Seventy-six protocols have employed retroviral vectors for the primary means of delivery. These RNA viral vectors are comprised of *cis*-acting long terminal repeats (LTRs) with pack-

Table 1. Time Interval to Obtain Approvals for Gene Transfer Protocols[a]

Agency approval	*Median time (months)*	*Range (months)*	*Percent >3 months*
IRB/IBC—RAC	3	0–9	29%
RAC—NIH Director	3	0–15	38%
RAC—FDA	7	0–26	74%
Final approval—first patient	3	0–>15	38%

[a]Based on complete responses for 55 protocols (time from IRB/IBC to RAC approval) to 80 protocols (time from RAC to NIH approval, RAC to FDA approval, and entry of first patient)

TABLE 2. DELIVERY VEHICLES FOR GENE TRANSFER

Delivery vehicle	*Number of approved protocols*	*Date first approved by NIH*	*Number of vector suppliers*	*Advantages of vector*	*Disadvantages of vector*
Viral					
Retrovirus vectors	76	3/89	23	Large capacity (7–10 kb) Easy to produce Efficient transfer	Targets only dividing cells Random DNA insertion Risk of replication
Adenovirus	15	4/93	8	Large capacity (7–10 kb) Targets non-dividing cells Transient delivery capacity Efficient transfer	Possible host immune reactions Risk of replication Transient delivery capacity
Adeno-associated virus	1	11/94	1	Less likely to produce immune reactions Targets nondividing cells Persistent delivery capacity	Risk of replication Small capacity (5 kb)
Nonviral					
Cationic liposome complex	12	4/92	7	Easy to produce No replication risk Less likely to produce immune reactions	Low efficiency
Plasmid DNA	2	11/94	2	No size limitation	Low efficiency
Particle-mediated	1	9/93	1	Easy to produce No replication risk Less likely to produce immune reactions	Low efficiency

aging capacity for up to 6–10 kb of foreign sequences. The minimum *cis*-acting LTRs are sufficient for replication and packaging of the vectors, which are then used to integrate the therapeutic gene into the target cell. While data are accumulating on the efficacy of these vectors in the clinic, the primary cellular target of the gene transfer must divide for efficient use of this vehicle. Although the numbers are still quite small, to date no evidence supports one of the initial concerns of this vector delivery system, that is, the potential for insertional mutagenesis.

Of the DNA viral vectors, adenovirus is currently the primary candidate for direct *in vivo* gene delivery. This vector, which also relies on complementation, still carries a significant portion of the viral genome (approximately 80%). While rendered replication-defective, this viral vector delivers the therapeutic gene in the context of the adenovirus genome, which typically comprises 30 kb of viral sequences. This vector has the capacity to infect nondividing cells and deliver the double-stranded genome to the nucleus in an episomal form. Typically, this vector does not persist for extended periods of time. It also has associated immunological consequences including potential induction of humoral and cellular immunity to transfected cells. These issues are still being addressed at the vector modification level. While the majority of the protocols using the adenovirus vector involve treatment of cystic fibrosis, it appears that this vector could play a critical role in the cancer gene therapy arena due to its efficient and transient delivery capacity.

The last of the DNA viruses approved for clinical use to date is the adeno-associated virus vector. This DNA vector, similar to the retrovirus system, carries minimum *cis*-acting sequences required for replication, packaging, and potential integration into the target cell. This vector is also capable of infecting nondividing cells similar to the adenovirus system. While approved by the RAC for use in cystic fibrosis trials, no clinical studies have been initiated with this system to date.

The remaining 13% of the gene therapy protocols have utilized nonviral delivery systems, such as cationic liposomes (11.3%), plasmid DNA (1.9%), and particle-mediated delivery (0.9%). Although these systems appear inherently more attractive due to their simplicity, usual inability to elicit adverse immune responses to the vectors, and ease of production, their efficiency in gene delivery appears to be lagging significantly behind the viral delivery systems. It is clear that in all of the approaches being used today, major improvements in the delivery systems are required for successful delivery of therapeutic genes in the clinical setting.

SUMMARY OF CLINICAL TRIALS BY CATEGORY OF PROTOCOLS

Human gene transfer protocols can be broadly subdivided into those carried out for the purpose of "gene marking" *versus* those carried out for eventual therapeutic intent ("gene therapy"). Gene marking protocols involve the insertion of a detectable biologically inert gene into cells *ex vivo* for the purpose of tracking the fate of the infused cells *in vivo*. The gene inserted is not chosen for any possible beneficial effect but simply as a "tracer" to localize the marked cells and determine their persistence. Twenty-five or 24% of gene transfer trials repre-

sent marking studies, with the remainder of the protocols considered under the category of gene therapy.

The broad category of protocols that could have eventual therapeutic implications has been divided here into subcategories according to the disease target. The disease categories include cancer, infectious diseases, monogenic inherited disorders, and other disorders (Table 3). The greatest number of protocols are targeted at the treatment of various types of cancer, although the largest number of protocols focused on treating a specific disease are for cystic fibrosis. The greatest number of patients treated so far have suffered from acquired immunodeficiency syndrome (AIDS) or from malignancies.

Gene marking studies

The initial gene marking studies were performed with retroviral vectors containing the cDNA for the neomycin phosphorotransferase gene (neomycin resistance gene, neo^R), which does not modify the function of the transduced cells but permits them to be detected at low frequency using polymerase chain reaction (PCR) techniques. Two general groups of marking studies have been conducted. The first group of protocols focuses on the transduction of leukocytes with potential antitumor activity (tumor-infiltrating lymphocytes, or TIL cells, and lymphokine-activated killer leukocytes, or LAK cells), whereas the second group focuses on the transduction of autologous bone marrow cells from patients with neoplastic diseases. (Rosenberg *et al.*, 1990, 1993; Brenner *et al.*, 1993a,b; Cornetta *et al.*, 1994; Deisseroth *et al.*, 1994; Rill *et al.*, 1994; Rooney *et al.*, 1995; Cai *et al.*, 1995).

In the first cell marking study (Rosenberg *et al.*, 1993), TIL cells were transduced with a neoR-containing vector and then infused into patients to determine the *in vivo* survival of the transduced cells and whether the TIL cells selectively migrated to tumor tissues. Analysis of 10 patients showed that the transduced cells persisted in the patients' peripheral blood during the first 21 days while exogenous Interleukin-2 (IL-2) was being administered. Once the exogenous IL-2 was discontinued, there was rapid clearance of the transduced cells. Sequential sampling of peripheral blood and tumor tissue did not demonstrate the presence of transduced TIL cells in tumor tissues at a time when transduced cells were not present in the peripheral circulation. No attempt was made to determine whether transduced TIL cells were also present in normal tissue. A second generation of marked TIL cell studies contains provisions for biopsy of both tumor and normal tissues to determine if the TIL cells selectively migrated to tumor tissues. The same investigators also evaluated the role of IL-4, as opposed to IL-2, in the *in vivo* maintenance of TIL cells. No results from the second-generation studies, however, have yet been published.

TABLE 3. SUMMARY OF RAC-APPROVED PROTOCOLS BY CATEGORY

Disease category	*Disease*	*Strategy*	*Number of protocols*	*Number of patients treated*
I. Gene Therapy			82 (76%)	501 (84%)
Monogenic inherited			20 (19%)	64 (11%)
	Alpha-1 antitrypsin deficiency	Replacement	1 (1%)	0 (0%)
	Chronic granulomatous disease	Replacement	1 (1%)	0 (0%)
	Cystic fibrosis	Replacement	11 (10%)	53 (9%)
	Familial hypercholesterolemia	Replacement	1 (1%)	5 (<1%)
	Fanconi anemia	Replacement	1 (1%)	0 (0%)
	Gaucher disease	Replacement	3 (3%)	0 (0%)
	Hunter syndrome	Replacement	1 (1%)	0 (0%)
	SCID-ADA	Replacement	1 (1%)	6 (1%)
Cancer			51 (49%)	214 (36%)
	Carcinomas, multiple types	Immunotherapy/*ex vivo*	23 (22%)	104 (17%)
		Immunotherapy/*in vivo*	7 (7%)	64 (11%)
		Pro-Drug	11 (10%)	36 (6%)
		Tumor suppressor	4 (4%)	1 (<1%)
		Chemoprotection	4 (4%)	8 (1%)
		Antisense	2 (2%)	1 (<1%)
Infectious Diseases				
	HIV		9 (8%)	219 (37%)
		Immunotherapy	6 (6%)	215 (36%)
		Replication Inhibition	3 (3%)	4 (<1%)
Other			2 (2%)	4 (<1%)
	Peripheral artery disease		1 (1%)	4 (<1%)
	Rheumatoid arthritis		1 (1%)	0 (0%)
2. Gene Marking			25 (24%)	96 (16%)
Cancer	Multiple malignancies	TIL/LAK cell therapy	6 (6%)	20 (3%)
	Leukemia, neuroblastoma	Autologous stem cell transplantation	17 (16%)	61 (0%)
Infectious Disease	EBV-lymphoma	Cytotoxic lymphocytes	1 (1%)	15 (3%)
Other	Acute hepatic failure	Liver transplantation	1 (1%)	0 (0%)

The second group of marking protocols have focused on the transduction of autologous bone marrow cells from patients with neoplastic diseases (predominantly acute leukemia, chronic myelogenous leukemia, and neuroblastoma). The purpose of these studies is to determine whether neoplastic cells present in unpurged autologous bone marrow contribute to relapse following bone marrow transplantation. In all disease settings, gene-marked tumor cells were found in relapsed patients. In no case, however, was the frequency of marked cells greater than 5%. Because the frequency of the initial transduction of the neoplastic cells was unknown, it was not possible to calculate the relative contributions of reinfused as opposed to residual host tumor cells to disease relapse. Nevertheless, it is clear that neoplastic cells that are present in unpurged autologous bone marrow do contribute to post-transplantation relapse (Brenner *et al.*, 1993a,b; Deisseroth *et al.*, 1994; Rill *et al.*, 1994). This result represents a tangible lesson that gene transfer technology can provide regarding the pathobiology of cancer. A subsequent series of studies is focusing on the comparison of different purging techniques prior to transplantation. In these studies, aliquots of bone marrow are purged by one or more techniques and then marked with neoR-containing vectors that can be individually identified by PCR techniques. The studies may demonstrate that one purging technique is superior to another.

An unexpected result of the autologous bone marrow marking studies has been new insights into normal hematopoiesis. Patients who received marked autologous bone marrow generally have had marked committed hematopoietic progenitors detected for up to 3 years following transplantation. This finding suggests that a relatively immature hematopoietic cell population, possibly true "stem cells," are being transduced. Marked T lymphocytes have also been identified; however, clonal analyses have not been performed to demonstrate the presence of identical integrants in both lymphoid and hematopoietic cells. Such a clonal analysis is essential to conclude unequivocally that pluripotent stem cells have been transduced. Nevertheless, the present studies demonstrate that immature hematopoietic and lymphoid progenitors can be transduced and that their progeny persist for several years. The initial frequency of transduced normal hematopoietic progenitors (CFU-GM) was as high as 20% (Dunbar *et al.*, 1995). Long-term transduction rates, however, have been between 1 and 5%. The initial high frequency of transduction is due to the fact that a significant proportion of "lineage-committed" hematopoietic progenitors are in cell cycle and, therefore, are susceptible to retrovirus-mediated gene transduction. The relatively low level of long-term gene transduction is consistent with the hypothesis that a relatively small proportion of immature hematopoietic cells are in cell cycle. The highest level of long-term gene transduction in normal hematopoietic progenitors was seen in the recipients of autologous bone marrow with acute myelogenous leukemia in remission. Immediately following the harvesting of the bone marrow, the cells were transduced for 6 hr without the addition of exogenous cytokines. The high levels of marked long-term cells suggest that the transduced cells were in cell cycle at the time of transduction. Because no exogenous cytokines were added, the high frequency of cells in cycle may be a consequence of the patients' prior chemotherapy.

The initial protocols to evaluate the contribution of nonpurged autologous bone marrow to post-transplantation relapse did not have as their primary goals the evaluation of normal hematopoiesis or the assessment of cell cycle status of immature hematopoietic cells. Nonetheless, significant scientific data

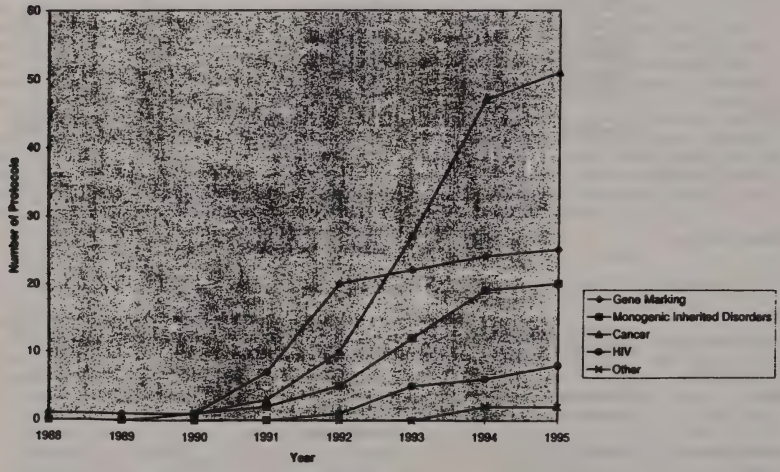

FIG. 1. Cumulative number of protocols in each category approved by the RAC.

concerning both basic and preclinical hematopoiesis has been obtained demonstrating that well-conducted clinical trials may have additional scientific benefits.

Cancer—immunotherapy treatment strategies

A variety of strategies involving transduction of human genetic material have been used in an effort to augment immune responses to cancer (Table 3). Although such approaches have been likened by some to "vaccination," these trials have all involved treating patients who already have cancer and hence such language is misleading. One type of immunotherapy strategy attempts to enhance the immunogenicity of in vivo tumor cells. The HLA-B7 and β2-microglobulin genes have been delivered by liposomes *via* direct injections into metastatic nodules for treatment of melanoma, hepatic metastases of colon cancer, and other tumors (Nabel *et al.*, 1993, 1994; Hersh *et al.*, 1994). A number of these studies have reported some gene transfer and expression, and one study noted tumor shrinkage in 6/15 patients with melanoma (Nabel *et al.*, 1993).

A large variety of *ex vivo* approaches have also been used to enhance the immunogenicity of cancer cells. In these protocols, cancer cells are cultivated *ex vivo* and transduced with genes expressing cytokines (IL-2, IL-4, GM-CSF, and/or interferon-γ) or HLA or tumor antigens. After transduction, the cells are reinjected into the patient. The genes have been delivered primarily by retroviruses, but a plasmid containing a bovine papillomatosis viral vector that creates an episome (using liposomes for transfection) and an AAV-derived plasmid liposome have also been used. The tumors have usually been autologous, but sometimes have been heterologous. The heterologous tumor cell line has been chosen either to match the donor HLA type or to be deliberately mismatched. Many protocols involve irradiation of the reinjected tumor to prevent its growth in the host. In one study, autologous tumor was used to stimulate the patient's own lymph node cells *ex vivo*, which were then to be reinjected into the patient.

Although some of these studies provided evidence of an immunological response to the intervention, and many directly injected metastatic nodules are said to have regressed, there is only 1 patient to date who might be considered to have had a significant systemic clinical response. This was a patient with melanoma who had his cells treated with an interferon-γ-expressing retrovirus. He has been described as tumor-free for 7 months. It should be noted, however, that melanoma is a tumor that has occasional spontaneous regressions and has historically responded to other immunological therapy (*e.g.*, BCG). Thus, success in a single patient does not imply the general utility of this approach.

Cancer—"Pro-drug"-based treatment strategies

After immunotherapy, the most common gene transfer approach to the therapy of cancer has been the "pro-drug" concept. All such protocols have involved the direct insertion of vector producing cells into an area of tumor. The gene inserted has been the herpes simplex virus thymidine kinase (HSV-TK) gene. Once this gene is incorporated intracellularly, it expresses a viral TK that makes the cell susceptible to killing by ganciclovir. Both animal studies and the relatively small experience in humans so far indicates that much of the potential beneficial effect of this approach occurs through a poorly understood "bystander" mechanism. That is, a much greater number of cells are killed by ganciclovir than actually receive the HSV-TK gene. It has been proposed that toxic metabolites of ganciclovir from those cells that have been successfully transduced pass to other nontransduced cells through gap junctions or other intercellular exchange mechanisms. In addition, it has been suggested that killing of TK-positive tumor cells with ganciclovir results in an improved immune response to TK-negative cells.

The primary target of these protocols has been glioblastoma, but other targets include leptomeningeal carcinomatosis, mesothelioma, and metastatic ovarian and breast cancers. All of these trials use a retroviral vector to deliver the HSV-TK gene, with the exception of one protocol, which will use an adenovirus that is injected intrapleurally to patients with malignant mesothelioma.

Several adverse medical events related to these studies have been reported. In most cases, these were thought to have resulted from natural disease progression or to the physical transfer procedures, rather than to a toxic effect of gene therapy *per se*. The major problem with the HSV-TK transfer procedure has been the injection of vector-producing cells into the cerebrospinal space, occasionally resulting in a significant but transient meningeal inflammatory reaction. One study reported some antitumor activity in patients with malignant glioma but these data are unpublished.

Cancer—Tumor suppression strategies

Four protocols reviewed by the RAC propose to inject patients with the p53 gene (wild type). Inasmuch as p53 is mutated in many cancers, wild-type p53 is thought to be a tumor suppressor gene. In one study, the investigators report that a single patient with squamous cell carcinoma is said to have shown marked tumor regression 1 month following gene transfer. The other three protocols are not yet fully approved.

Cancer—Chemoprotection strategies

This approach, represented by four protocols, uses retroviral vectors to introduce multidrug resistance genes into patients' hematopoietic cells as a means of protecting against chemotherapy-induced bone marrow suppression. In this way, it may be possible to increase the dose and frequency of chemotherapy. Although reports are preliminary, only very limited transduction of the gene has so far been found *in vivo*, perhaps emphasizing the critical investigative need for better understanding of the basic biology of gene transfer.

Cancer—Antisense RNA strategies

Two protocols have been proposed using an antisense strategy to prevent expression of oncogenes that are associated with specific carcinomas. One uses a retrovirus to deliver an antisense gene to "turn off" c-*myc* and c-*fos*, which are overexpressed in breast cancer; the other employs liposome-mediated anti-sense RNA to inhibit IGF (a tumor growth factor) in irradiated glioblastoma cells, which are then reinjected into the patient. To date, only 1 patient has been treated in this way, with no evidence of either cellular or humoral response.

Infectious diseases

Nine protocols have been developed for treatment of HIV infection: eight were reviewed and recommended for approval by the RAC, and one was supported solely by private industry and did not require RAC review (Table 3). The protocols fall into two general categories: those designed to test the ability of recombinant reagents to enhance immune responses to HIV and those involving the delivery of vectors whose products could suppress virus replication.

Six protocols are immunotherapeutic in nature. One investigation extends earlier work regarding the potential value of adoptive transfer in bone marrow recipients of cytotoxic T cells (CTLs) specific for cytomegalovirus (Walter *et al.*, 1995). This study examines the effects of HIV-specific CTLs that have been marked by *in vitro* transduction with a retrovirus-expressing a fusion protein. The fusion protein renders cells resistant to hygromicin and sensitive to ganciclovir, enabling selection of transduced cells with hygromycin. The ganciclovir sensitivity provides a fail-safe mechanism; the cells can be eliminated if unforeseen harmful effects occur. The investigators report evidence of gene expression in target cells *in vitro*. Most importantly, they documented transfer of retrovirally marked CTLs and preliminary evidence of an immunotherapeutic effect in transiently reducing HIV burden.

In a clever modification of this work, investigators are transferring HIV-specific CTLs transduced by retroviruses to express a CD4-zeta-chain fusion protein, a chimeric universal T cell receptor, allowing killing of a broader array of HIV-infected target cells through these gene-altered CTLs.

A Phase II study to determine the safety and immunotherapeutic potential of a retroviral "vaccine" for HIV in a large, multicenter study will enroll 168 patients. A vector expressing HIV-1 envelope protein is injected intramuscularly with the aim of inducing expression of the protein by myocytes and thereby enhancing virus-specific immune responses. Three Phase I studies have been conducted revealing the apparent good tolerance of the injections and limited *in vivo* evidence of enhanced HIV-specific immune responses. The particular data are confidential. Enthusiasm generated for these Viagene studies by their rapid pace and entry into Phase II is tempered by the reality that it may not be possible to augment HIV-specific immune responses in a meaningful way in individuals who are already immunologically impaired and who have progression of their disease, despite chronic exposure to high levels of the envelope protein.

Three protocols are poised to explore molecular tools to down-regulate HIV replication. In one study, $CD4^+$ T cells are infused after *in vitro* transduction with vectors expressing the gene for REV, a dominant inhibitory form of a protein that usually enhances HIV-1 replication. A second protocol involving a similar construct and an additional inhibitory moiety, an antisense TAR transcript, is awaiting initiation. In the third protocol, investigators aim to infuse $CD4^+$ T cells that are transduced *in vitro* by retroviruses to express a ribozyme that cleaves HIV-1 RNA.

All three approaches inhibit HIV *in vitro*. They are designed to achieve a resident population of CD4 cells that are refractory to HIV replication in the patients studied. Unless such cells could expand to a sizable fraction of the circulatory cell pool, effects on HIV cannot be documented. Promising Phase I studies could, however, lead to transfer of similar recombinant reagents into lymphocyte progenitor cells.

Monogenic inherited diseases

Early on, it was thought that the RAC would deal primarily with the safety aspects of gene therapy specifically for monogenic genetic diseases, with the expectation that these diseases would be most amenable to gene therapy. The promise of molecular genetics has always held the hope that normal genes could be inserted into cells of an affected host in which they would express their normal gene product, thereby curing or at least ameliorating an underlying genetically determined disease. Such an approach might theoretically only require a single treatment if a normal gene could be inserted into stem cells, so that all descendants of the engineered stem cell would carry out their normal function.

Currently, however, only 24% of the gene transfer protocols with therapeutic intent approved by RAC are directed at monogenic diseases in contrast to 62% targeting cancer and 11% HIV infection. Despite the fact that monogenic genetic disorders are potentially more amenable to cure through gene transfer, they are rare and, therefore, affect a much smaller percentage of the population than cancer or HIV. Cancers and HIV, on the other hand, appear to be far more difficult to treat with gene transfer, but they occur much more frequently and have, therefore, attracted the greater interest of the biotechnology industry. Two other aspects of the move toward tumor and HIV therapy rather than monogeneic inherited diseases were that: (i) the latter are, to a great extent, pediatric illnesses, raising an ethical question of whether gene therapy should be tried on adults before children; and (ii) the seriousness of the condition for cancer and HIV patients could justify extreme measures, such as gene therapy.

Gene therapy experiments have been directed at eight different monogenic inherited diseases. (Table 3) In only three of these (adenosine deaminase deficiency, homozygous familial hypercholesteremia, and cystic fibrosis), however, have human trials actually been conducted. The first example of gene therapy in humans was undertaken in ADA deficiency by transferring the gene encoding the ADA enzyme into the T lymphocytes of two affected children using a retroviral vector (Kohn *et al.*, 1995; Kohn, 1995; Blaese *et al.*, 1995). ADA deficiency is an extremely rare autosomal recessive disease that causes severe immunodeficiency leading to childhood death from overwhelming infections. Repeated infusions of the gene-modified T lymphocytes led to increased numbers of T cells and increased ADA levels in circulating T cells, as well as partial immune reconstitution; in addition, expression of the ADA gene persisted for a 2-year period. The results of gene transfer in these initial experiments with lymphocytes as the target were encouraging, because they appeared to result in improved health of the two children treated (Blaese *et al.*, 1995). Therefore, other investigators (under the same protocol) have also inserted the ADA gene into hematopoietic stem cells that can remain in blood circulation for long periods of time and have administered such treated stem cells to three infants through their peripheral cord blood (Kohn *et al.*, 1995). So far, the ADA gene continues tobe expressed in T cells after 18 months. At the present time, however,

definitive assessment of the clinical efficacy of this ADA gene therapy is difficult because all patients treated by gene therapy also continue to receive enzyme therapy with mono-methoxy-polyethylene glycol-bovine ADA (PEG-ADA), that in itself, provides clinical benefits.

Five patients with homozygous familial hypercholesterolemia have been treated with gene therapy (Grossman *et al.*, 1994, 1995; Raper *et al.*, 1996). This disease, caused by a defective or absent low-density lipoprotein receptor gene, is very rare and results in very high cholesterol levels in childhood and adolescence, leading to coronary heart disease and death early in life. According to the protocol, 15–20% of the liver is removed by surgery and normal low-density receptor genes are transferred into the patient's liver cells *ex vivo* using a retrovirus vector. These cells are then reinfused into the patient's remaining liver *via* the portal vein. Results showed limited gene expression (approximately 5%) in hepatocytes from liver tissue that were harvested 4–6 months after gene transfer in all 5 patients. A significant reduction in the elevated low-density lipoprotein cholesterol level (LDL) was reported in 1 patient. However, several prominent lipidologists questioned whether the beneficial results might not be ascribed to the endogenous synthesis of the patient's own LDL cholesterol due to the experimental manipulation rather than to gene therapy, especially because the LDL receptor gene mutations in this patient were mild and could have responded to experimental treatment other than the inserted gene (Brown *et al.*, 1994). When the investigators used the same approach with patients (all children) with more severe mutations of the LDL receptor gene they showed that 1 additional patient had decreased LDL levels, but that there was no appreciable effect in the other patients.

Most of the work in gene therapy for single-gene inherited disease has focused on cystic fibrosis (CF), the most common autosomal recessive disease in Caucasians in the United States (1 in 2,000). Recurrent pulmonary infections and other complications lead to progressive respiratory compromise and results in death, often before the age of 30 years. The approach, used in the 11 different protocols (by eight different investigators) and applied to 53 patients, is to transfer the normal membrane channel gene that is defective in cystic fibrosis (*CFTR*) into cells of the respiratory tract. Almost all of the investigations have used adenoviruses as the vector. One study, approved by the RAC, but pending FDA approval, proposes to use a liposome vector. Results of ongoing trials have shown that the normal gene was transduced and expressed in some CF cases, but evidence of its normal function was not found uniformly (Zabner *et al.*, 1993; Crystal *et al.*, 1994; Dodge, 1995; Knowles *et al.*, 1995). One patient showed initial pulmonary toxicity of the gene therapy, but this complication appears to have been avoided subsequently by reducing the dose of the transferred gene (Crystal *et al.*, 1994). Thus, at the present time, in a minority of CF patients treated, the transferred gene has been expressed in a clinically relevant location for times between 4 and 9 days. However, biological and clinical improvement cannot yet be evaluated. It should also be noted that if successful, this approach to the treatment of cystic fibrosis would require periodic readministration of gene therapy because transduction of an appropriate stem cell population is not involved. This could limit the value of adenoviruses as vectors of the CFTR, because host immune responses to the virus are also likely to mount with multiple treatments. One encouraging aspect of the cystic fibrosis protocols has been rapid communication of results from one investigator to another in terms of potential toxicities of gene therapy, in part expedited by the RAC and FDA as well as the investigators themselves. Adventitial production of replication-competent adenovirus in stocks (but not clinical material) also has been noted by three groups, thus demonstrating the need for continued vigilance on this front.

Overall, only relatively minor toxicities have been encountered in these gene transfer trials with therapeutic intent. Encouraging clinical results have been suggested by these trials, but simultaneous use of alternate effective therapies and the unknown effects of dramatic surgical interventions on endogenous gene function make it impossible at the moment to know the true beneficial effects from the clinical perspective. The controversy surrounding the trial for hypercholesterolemia illustrates the principle that since each genetic disease poses different problems of pathology, physiology, biochemistry, and clinical medicine, it is not only difficult to predict potential toxicities but also difficult to design generically applicable initial experiments.

Other disorders

Two protocols are directed to disorders that are not conveniently subsumed into one of the other disease categories. One protocol approved by the RAC for the possible treatment of rheumatoid arthritis entails the transfer of an antiarthritic cytokine gene (IRAP) directed into affected joints. It has not yet enrolled patients. A second protocol for treating arteriosclerosis by transferring an angiogenic gene into peripheral occluded arteries with the aim of stimulating collateral circulation has now entered 3 patients. Unpublished reports suggest the possibility of efficacy in 1 of these patients, evaluated by pre- and post-angiography. Although one can reasonably determine that toxicity has been minimal or absent in this protocol, it is still too early to assess clinical efficacy.

SUMMARY

Clearly, gene transfer therapy has caught the interest, imagination, and hope of the public, industry, and academia. The most remarkable and compelling aspect of the clinical applications of this technology so far has been the lack of significant toxicity directly related to gene transfer in the numerous Phase I trials. It is important to recognize that problems, such as the production of replication-competent retroviruses and the possibility that adenovirus-containing recombinant agents will shed and spread remain of concern. However, the current regulatory approach has been adequate to prevent significant new problems in these early trials.

Gene marking protocols have advanced the science of autologous transplantation and may be expected to be part of experimental evaluation of new approaches to transplantation for the next several years. The most important finding of the marking trials for the future of gene therapy is that genes may be expressed *in vivo* in hematopoietic progenitors—immature stem

cells that are the source of succeeding generations of circulating blood cells. Effective transduction of stem cells would enable the maintenance of genetic reagents in the human body for several years or even, possibly, for the life-time of the individual.

It is clearly too early, however, to assess the therapeutic efficacy of gene therapy or even to predict its promise. Numerous studies have reported the ability to express recombinant DNA *in vivo*, but few have reported clinical efficacy. Gene therapy is still at an early stage and nearly all of the studies consist of Phase I trials, with the goal of establishing safety, rather than efficacy, of the procedure. It is difficult to discern whether the small number of cases of clinical improvement are directly attributable to gene therapy or merely to spontaneous remission of disease or to other forms of medical intervention provided simultaneously with gene transfer. The few "dramatic" successes claimed are not dissimilar to those that were reported with a variety of other therapeutic techniques for which enthusiasm ultimately dampened over time. This is not to say that gene transfer therapy is a failure or that it should be abandoned. Rather, the data presented in this report emphasize that even after 5 years of clinical work, there remains a need for a further effort directed at improving the basic technology.

Recognizing the problems so far in demonstrating clinical efficacy and the necessity of establishing a clear focus for the field, the Director of the NIH established a panel of experts (Orkin and Motulsky, 1995) to provide recommendations regarding future NIH-sponsored research in human gene transfer. In addition to stressing the need for greater scientific rigor, with the development of well-defined experimental hypotheses and quantifiable molecular and clinical end points as the underpinning of future studies, the panel has emphasized the need for effort in three areas. The first is the development of vector technology and an understanding of the biological interaction of vectors with the host. Vectors need to be developed to increase and maintain an adequate level of gene expression in somatic cells over prolonged periods to achieve cell-specific or tissue-specific expression and to regulate gene expression within the cell. The second area to be developed is a basic understanding of disease pathogenesis. Defining the mechanisms by which gene mutations lead to disease would be a crucial step toward conceptualizing new treatment strategies. Furthermore, knowledge of disease pathophysiology should lead to better understanding of which cell types in the body are appropriate targets for effective therapy, what levels of gene expression are required for clinical effectiveness, and how to regulate gene expression once genes have reached the target cells. The third area recommended by the panel is the future development of animal models, both of naturally occurring and genetically altered animals, to test experimental hypotheses and specific therapies prior to trials with humans. The panel likened the progress of gene therapy to that of bone marrow and organ transplants, which required several decades of trial and error before reaching its current status of acceptability for patients with life-threatening disease.

In sum, while the public has anticipated that this new form of therapy will lead to novel medical cures, it is still too soon to tell if and when gene therapy will achieve its goals.

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Mr. WALTERS. We knew already in 1995 that we were reaching the limits of manual systems for tracking what was happening in gene therapy. In fact, some staff members at NIH told me they almost died during that 6 months of reviewing and gathering information for the June meeting.

From my perspective, Federal oversight during the early years of gene therapy worked reasonably well, with some minor tensions between NIH and FDA. However, I think we have seen, especially since September of last year, that the oversight system is failing us and that serious problems have arisen. There are a variety of reasons for that, and we can go into them in the discussion if you would like.

I would like to compliment Paul Gelsinger for helping to bring our attention to some of these problems. He has remained engaged in the discussion of this topic, and I very much appreciate what he has done.

I would also like to express appreciation to you and to Congressman Waxman for your letters to NIH, which also have revealed additional information.

In the same context, I think we owe a great deal to the press because investigative reporters have dug out a great deal of information and indeed, have helped to reveal the extent of the oversight problem.

From my point of view, there are five major problems in the current oversight system, and I will mention them very quickly. First, there is no computerized system that has been developed at NIH for tracking what happens to patients in gene therapy studies. We have known for at least 5 years that that system was needed.

Second, only a small fraction of serious problems that arose in gene therapy studies were reported to NIH and the RAC before October of last year. It was only in response to a crisis that we have had the outpouring of new reports. Between 5 and 6 percent of those reports had been made before the crisis occurred.

Third, on several critical matters, there has been a lack of appropriate cooperation between the FDA and the NIH. New modes of cooperation have been started in response to a crisis, especially in December of last year—but my question is why couldn't those procedures have been put in place at least 2 years earlier.

Fourth, the FDA itself may not have adequate staff to cover all the problems that may be encountered by patients in gene therapy studies. It is a burgeoning field. In addition, I am not sure that we should expect one regulatory agency alone to perform the early warning role when patients begin to experience unanticipated side effects.

And fifth, there continue to be serious problems of disclosure and informed consent in some gene therapy studies. Patients are often not told how young this field is and how unlikely that they, the pioneers in the research, will actually benefit from taking part in the research.

A former RAC member, Ms. Abby Meyers, published an eloquent op-ed article on this topic in last Sunday's Washington Post. Her article was entitled: "A Lot of Rules, Too Many Exceptions." I

would like to ask the subcommittee's consent to have her article appended to my testimony.

Senator FRIST. Without objection.

[The document referred to follows:]

A LOOK AT . . . Informed Consent

A Lot of Rules, Too Many Exceptions

By Abbey S. Meyers

Sunday, January 30, 2000; Page B03

The highly publicized death in September of an 18-year-old patient in a clinical trial at one of the largest academic gene therapy centers in the world--the University of Pennsylvania's Institute for Human Gene Therapy--has spurred a host of investigations and recriminations. It has also prompted some people to ask a question we shall never be able to answer for sure: If Jesse Gelsinger had known that monkeys had died from the therapy before it was given to humans and that several previous participants had suffered serious toxic reactions to the kind of treatment he was volunteering to undergo, would he have agreed to take part in the trial?

More generally, can we be certain that participants in the proliferating number of experiments being conducted in other centers around the country have been given the information they need before agreeing to participate?

My experience as a former member of the National Institutes of Health advisory committee that oversees gene therapy research suggests that the likely answer to both those questions is no. Gelsinger's untimely death has exposed the shortcomings in the system we have developed to protect patients. Some researchers seem to view the process of informing patients about experiments as a necessary hindrance in their race for scientific glory--and financial reward. Gelsinger's story is viewed by many as an aberration. I believe, however, that it may fit a pattern. Some researchers--not all--don't take seriously enough the need for informed consent, despite the abuses of the past.

Certainly, many of the greatest triumphs of the past 100 years were the accomplishments of medical researchers who tamed rheumatic fever, eradicated smallpox and polio and discovered the magical potency of antibiotics to win countless victories over disease and death.

But for every story of medical success there is a darker one of medical abuse: the Nazi experiments on defenseless minorities; the Tuskegee experiment in which African American men with syphilis were purposely denied medical treatment for decades by American physicians; and numerous unethical experiments on the mentally retarded and mentally ill who were confined to U.S. institutions. History teaches that we should be cautious about allowing researchers to pursue their investigations without government oversight and regulation to ensure that their research will be meaningful and patients will be adequately protected.

The Nuremberg trials revealed the full horror of medical experiments conducted by Nazi scientists during World War II--and created the political resolve in industrialized countries to establish rules that would protect human subjects in all future clinical experiments. In the United States, this code of conduct for scientific research became

known as the "Common Rule," and it was last revised by the federal government in 1981.

The Common Rule requires that all patients--or their legal guardians--who volunteer to participate in clinical trials be fully informed about the details of the experiment. They must have a complete understanding of the risks (even the possibility of unknown dangers) as well as the potential benefits of the experiment. For example, in an early (Phase I) clinical trial, which is conducted solely for the purpose of determining the safety (not the effectiveness) of a treatment, volunteers must be told that they should not expect any personal benefit from the experiment, although the knowledge that scientists will gain from the trial is likely to help other patients in the future. In essence, the motivation for participation must be altruistic--a desire to help humanity, not a desire to help oneself.

The National Research Act of 1974 led to legal protections for all volunteers who participate in medical and psychological research that involve federal funds. The responsibility for ensuring that these rules are obeyed is assigned to an institutional review board (IRB) located at every facility in the United States that conducts research on humans, as long as the institution receives federal money. Privately funded research is not affected. The IRB must ensure that each experiment is scientifically and ethically sound, and must monitor its progress to ensure that patients' rights are adequately protected. Unfortunately, IRBs have been overburdened and underfunded. In recent months, the federal government has stopped all human research at several universities--including Duke University Medical Center, Rush-Presbyterian-St. Luke's Medical Center in Chicago, and West Los Angeles Medical Center--because their IRBs were failing to comply with patient protection rules.

These sorts of shortcomings are particularly troubling in the swiftly moving field of gene therapy. If the example of Gelsinger is anything to go by--and the closings of these other medical centers suggests it is--patients are not being fully and truthfully informed before being asked to give their consent to participate.

Unlike the infamous experiments that led to the adoption of the Common Rule, modern gene therapy research is primarily funded by private companies, not the government. That's an important distinction. While government-funded academics must share information about their experiments, corporate funding often requires scientists to keep information secret: Companies often insist that releasing research information may provide an advantage to their competitors. If they release news, it is often carefully tailored good news, while the bad news remains hidden in the "trade secret" closet.

The result is that many people have the mistaken impression that gene therapy is already curing people (so far, however, there have been no documented cures), and pin false hopes on the technology. Cancer patients, for example, will often demand admission into a gene therapy trial because it represents their "last chance" to be cured. It is worth noting that the great majority of gene therapy experiments are not conducted on genetic diseases, which are too rare to encourage investment capital, but on cancer, primarily because investors sense that a potential treatment for cancer will be more profitable.

Gene therapy has always been a controversial area of science, because it has the potential to change the essence of the human race. In recognition of this, the government assigned the Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health (NIH) the task of overseeing development of the technology. Composed of volunteer scientists, expert bioethicists, consumer advocates and others who discuss each trial at quarterly public meetings, the RAC created rules called "Points to Consider." Gene therapy researchers must obey these rules if any patients in the trial are treated at a hospital that receives federal funds. But trials sponsored by private companies do not have to obey the rules if patients do not use facilities receiving federal funds.

There have been a number of problems with putting those rules into effect. When members of the RAC have complained that an informed consent document is inaccurate or misleading, they are reminded that only the local IRB has authority to dictate the words in the document. Not even the Food and Drug Administration has any authority over the wording. (The agency focuses solely on science, not ethics, so it cannot demand that a doctor disclose to patients in a trial that he or she owns shares in the sponsoring company and thus stands to benefit financially from the product being tested.) The sole authority for approving informed consent documents--the local IRB--is not required to have any members who are knowledgeable about the technology that they are reviewing.

Members of an IRB (mostly staff of the institution) are usually keenly aware of the need to attract government and industry research grants, and often are unwilling to be too demanding when asked to revise informed consent documents. It sometimes appears that IRBs are more concerned about protecting their institutions' liability concerns than about protecting patients.

In 1994, the RAC's Working Group on Informed Consent strengthened the Points to Consider rules and spelled out exactly what each consent document should address. Of course it is a challenge to make the highly technical work of modern research scientists comprehensible to patients, but the Points to Consider set up some straightforward rules: They require that informed consent documents must be written in understandable language and they state that any adverse effects seen in animal studies and patients who previously participated in the experiment must be disclosed. Nevertheless, researchers and IRBs largely continue to ignore these rules. The FDA, which does not have any bioethicists on its staff, continues to approve new trials with inadequately worded informed consent documents.

In recent years, the RAC's authority over gene therapy research has also lessened. In 1996, Harold Varmus, as director of the NIH, withdrew the RAC's authority to approve gene therapy protocols, which greatly diminished its oversight. Today, the RAC is left with only moral suasion, especially with regard to informed consent documents.

After Jesse Gelsinger died from multiple-organ failure, brought on by the infusion of genetically altered cold viruses into his diseased liver, the FDA found some glaring violations. The informed consent document Gelsinger signed was very different from

the documents the RAC had reviewed, and even different from the so-called "final" document that the FDA had seen. Information about the deaths of monkeys in the pre-clinical studies had been deleted, and there was no mention of several serious adverse events experienced by patients who preceded Gelsinger in this trial. As a result, all seven of the University of Pennsylvania's gene therapy studies were recently suspended.

Some of these problems were undoubtedly peculiar to this trial. But the oversight system failed to prevent serious violations of patient protection rules. Gelsinger's death shows that we must take a closer look at these guidelines. After all, gene therapy is only one of many burgeoning biomedical advances. Soon xenotransplantation, stem cells, cloning, in-utero transplants, fetal gene transfers and many as-yet unimaginable giant steps in medicine will be approaching the clinic.

Next week, as a result of the investigations into Gelsinger's death, there will be congressional hearings on gene therapy trials. Now is the time to build the political resolve to fix this problem, before more tragedies occur. We should not allow the Gelsinger case to stop the progress of gene therapy research. The research must move forward with the appropriate patient protections firmly in place to ensure that all clinical trial volunteers are fully informed before they are asked to give their consent.

Abbey Meyers, the founder and president of the National Organization for Rare Disorders, was a member of the National Institute of Health's Recombinant DNA Advisory Committee's (RAC) Gene Therapy Subcommittee from 1989 to 1992, and a member of the full RAC from 1993 to 1996.

Even Before Nuremberg

The Nuremberg Code of 1947 is usually referred to as the prototype for regulations regarding informed consent, but debate over medical experimentation goes back to 19th-century Prussia. In 1898, a University of Breslau professor of venereology named Albert Neisser injected serum from syphilitic patients (most of whom were prostitutes) into patients being treated for other conditions. The patients were not informed about the injections nor asked for their consent. When some of them contracted syphilis, Neisser denied his trials were the cause. But news of his experiment prompted a public outcry.

Berlin psychiatrist Albert Moll was one of the few academic physicians who did not side with Neisser at the time. He collected evidence from 600 cases of unethical, non-therapeutic research on humans and called for a new practice: informed consent. Neisser was fined for his actions by the Prussian Royal Disciplinary Court, according to a 1996 account by the British Medical Association.

After the court's action, the Prussian government formed a commission to study the matter further. In 1900, Prussian hospitals and clinics were ordered to perform medical interventions only for diagnosis, healing and immunization-- unless "the human subject was a minor or not competent for other reasons" or if the subject "had not given his or her unambiguous consent" after "proper explanation of the possible negative consequences" of the intervention. Unfortunately, the directive was not legally binding, which could account for its lack of historical impact.

Thirty years later, the Nazi government issued legal guidelines, based on a doctrine of informed consent, that were meant to minimize risk for human subjects. The wording was remarkably similar to informed consent documents today. The guidelines obviously did not keep Nazi doctors from performing unethical experiments on concentration camp prisoners during World War II. The ethical regulations in human medical research--and the doctrine of informed consent that came about as a result of the Nuremberg trials--were the ones with staying power.

Cases

Judgment calls about how and when to pursue informed consent are often controversial. Examples in the news during the late 1990s:

* At a hospital in Philadelphia, doctors treating a 31-year-old man with a particular type of benign brain tumor recommended an untested variation on the usual course of radiation. They did not get the man's consent; he suffered an incapacitating stroke after the treatment. The neurosurgeons had not sought experimental status for the procedure, nor had they submitted their proposal to a hospital review board until they had treated several other patients, more than a year later. A malpractice suit against the doctors and the hospital is set for trial in mid-February.

* One hundred severely injured trauma victims admitted to emergency rooms across the country were unwitting participants in a drug company's clinical trial for a new blood substitute intended to aid patients in hemorrhagic shock. The product was used to treat 52 patients categorized as having a high expected mortality rate due to their injuries; 24 died, leading the manufacturer to stop the trial. Under government rules, the trial was legal; an FDA waiver allowed the drug company to test its product on trauma victims who are unconscious or otherwise unable to give consent. The hospitals conducting such trials are supposed to notify their communities well in advance. A similar trial using the same blood substitute is ongoing in European hospitals.

Mr. WALTERS. As a Nation, I think we can do better in protecting human subjects in gene therapy studies than we have done during the past 10 years and especially during the past 5 years. The death of a generous young man, the serious side effects experienced by several and perhaps numerous other subjects, and the almost total breakdown of the system for reporting serious adverse events to the RAC should be a wake-up call to us all.

I have five recommendations. First, we need to strengthen the one public advisory committee for gene therapy research, the NIH RAC. This committee has a 25-year track record and an international reputation for integrity and independence. Interested members of the public can attend the meetings of the committee or communicate their views to the committee and its staff by phone, letter, or electronic mail.

Second, the NIH and the RAC should create a Data and Safety Monitoring Board specifically for human gene therapy research. The primary role of this board would be to identify problems being encountered by patients in gene therapy studies and to act promptly to notify researchers and other patients when necessary. It would also provide regular reports to the RAC and to the public.

Data and Safety Monitoring Boards are becoming a standard feature of high-quality clinical research in cooperative cancer trials. In the Women's Health Initiative clinical trial, there is a Data and Safety Monitoring Board; in many studies of individual drugs, there are Data and Safety Monitoring Boards. I think we should do no less for the volunteers who take part in gene therapy studies.

Third, the RAC and the Data and Safety Monitoring Board will require help to do their jobs well. They will need a staff or a coordinating center skilled in gathering information from multiple research centers and in entering the information into online databases. In some cases, clinical experts will need to analyze which problems resulted from a patient's underlying disease and which problems resulted from the gene therapy procedure itself.

An expanded RAC staff could also be helpful to gene therapy researchers at a much earlier stage in the whole process when studies are being planned. For example, RAC staff members could help researchers prepare consent forms that are candid, clear and balanced.

Fourth, thus far, the RAC, the NIH and the FDA have been asked to provide oversight for gene therapy research on their own, without much assistance from the Secretary of Health and Human Services. In my view, the Secretary needs to become more actively involved in gene therapy research and especially in ensuring that the NIH and the FDA cooperate fully in their respective roles.

Finally, the Congress itself may want to look at the appropriate role for the RAC within the executive branch.

Within the past 6 months, gene therapy research has taken on important, symbolic significance in the United States. In some ways, public confidence in this important field has been shaken, and public trust in the integrity of leading researchers in the field has been strained. One way to mark a new beginning would be to move the RAC and its staff to a more prominent and more visible position within the Federal Government—perhaps to the office of

the Secretary of Health and Human Services. I suggest that in part because Secretary Shalala's office is increasingly becoming the focal point for our national effort to protect human research subjects.

From this new position, the RAC could then provide annual reports on gene therapy research, not only to the Secretary, but also to the Congress, the President and the Nation.

Mr. Chairman, the task that we are involved in today is a worthy and indeed a noble task. We are attempting to respond to system failures and the tragic death of an altruistic young man. We are trying to devise a better plan for overseeing gene therapy research in the future. If we are committed to doing this job well, I am convinced that we can create a new model for protecting the human subjects who make this research possible.

If this model succeeds, public confidence in gene therapy research will be restored, and the great promise of this important area of research will, I believe, begin to be realized. If the model succeeds, we will also have made an important contribution to the future of biomedical research. When the next major biomedical technology emerges, we will be poised to oversee its development in a more effective and a more respectful manner.

Thank you. I would be happy to answer questions.

Senator FRIST. Thank you, Dr. Walters.

[The prepared statement of Mr. Walters follows:]

PREPARED STATEMENT OF LEROY WALTERS, PH.D., DIRECTOR, KENNEDY INSTITUTE OF ETHICS, GEORGETOWN UNIVERSITY

Mr. Chairman and Members of the Subcommittee: Thank you for inviting me to discuss ethical issues in human-gene-therapy research. I appreciate the opportunity to be a participant in this important hearing.

My name is LeRoy Walters. I have been a faculty member of the Joseph and Rose Kennedy Institute of Ethics (as it is now called) at Georgetown University since 197 1. It has been my privilege to be a member of the NIH Recombinant DNA Advisory Committee (RAC) on three separate occasions—from 1976 to 1980, from 1984 to 1988, and from 1992 to 1996. From the beginning of 1993 to the end of 1996, I served as Chair of the RAC. I have had a long-standing interest in the ethical issues surrounding gene-therapy research. In 1997 a coauthor, Julie Gage Palmer, and I published a book entitled *The Ethics of Human Gene Therapy.* [1]

Two Eras in the Early History and Work of the NIH Recombinant DNA Advisory Committee (RAC): 1974–1983 and 1984–1990

The NIH RAC has had a long and distinguished history. It was initially established in the fall of 1974, shortly before the Asilomar meeting on research with recombinant DNA. The committee met for the first time in February of 1975, immediately after the Asilomar meeting. From that moment until the early 1980s the RAC set the safety standards for all recombinant DNA research being conducted in the United States. These standards became known as the NIH "Guidelines for Research Involving Recombinant DNA Molecules." The NIH guidelines were adopted, in whole or in part, by many other industrialized countries.

In the early years most recombinant DNA research was funded by NIH and NSF, so academic researchers had little choice but to follow the "Guidelines." However, private companies also voluntarily complied with the RAC's guidelines, in part to avoid regulation by their states or municipalities. While Congress considered numerous bills that would have regulated recombinant DNA research, especially in 1977, in the end the Congress deferred to the NIH and the RAC.

By about 1980, it was clear that most kinds of laboratory research with recombinant DNA were safe for both laboratory workers and the environment. New questions arose, such as the use of recombinant DNA techniques for large-scale production of human insulin and the deliberate release of recombinant DNA into the environment, for example, to lower the temperature at which strawberry plants freeze.

[1] New York: Oxford University Press, 1997.

These new technologies gradually moved to the appropriate regulatory agencies, the Food and Drug Administration and the Environmental Protection Agency.

By 1983 it seemed as if the RAC's advisory role might no longer be needed. By a strange and perhaps fortuitous quirk of history, a new technique called "human gene therapy" was just beginning to be developed. There was a certain degree of continuity with the past. After all, gene therapy was, from one perspective, the introduction of recombinant DNA (or products derived from recombinant DNA) into human beings. However, gene-therapy research was clearly a hybrid field. On the one hand, it was highly technical and required the expertise of molecular biologists and human geneticists. On the other hand, gene-therapy research was human-subjects research, which was governed by its own set of rules and which was quite comprehensible to laypeople.

In 1982 a report by a presidential commission on bioethics, Splicing Life, and a congressional hearing on "Human Genetic Engineering" had framed the major ethical issues in gene-therapy research. In response to those hearings, the NIH and the RAC began in 1983 to consider whether the committee should volunteer to review genetherapy research protocols on a case-by-case basis. Over the course of a year the NIH and the RAC moved step-by-step toward accepting the oversight of gene-therapy research, in part because its other work was essentially finished and in part because no other agency or committee was prepared at that time to review this emerging field of research. A working group on human gene therapy was established during the summer of 1984 as a subcommittee to the RAC, and this working group began developing guidelines for gene-therapy research in the fall of that year. (I was privileged to chair that working group from 1984 to 1991.) Once again, the Congress deferred to the executive branch and to its public advisory committee, the RAC. It did not pass legislation regulating gene-therapy research, nor did it establish a presidential advisory committee on the "Human Applications of Genetic Engineering," as recommended by Congressman Albert Gore, Jr., in H.R. 2788 (April 27, 1983). The Congressional Office of Technology Assessment also published a report in late 1984, Human Gene Therapy. Background Paper, that seemed to accept the merits of the approach being taken by NIH and the RAC.

What were the central ethical questions to be asked about any proposed genetherapy research protocol? In my view, the many questions asked in the RAC's guidelines—the "Points to Consider" document—can be reduced to four rather simple and straightforward questions:

1. What are the potential harms and benefits of the research to the research subjects who will participate in a planned study?

2. How will these potential harms and benefits be communicated to prospective research subjects, so that they can make voluntary and informed decisions about whether to participate in the research?

3. How will the selection among potential research subjects be made in a fair and equitable way, especially in cases where more people want to participate than can be enrolled in a study?

4. How will the privacy of research subjects be protected and the confidentiality of their medical information preserved?

If it is possible to develop guidelines for an emerging field of biomedical research too early, the RAC and its working group did so. We hurried to finish polishing the "Points to Consider" document in the spring and summer of 1985, then had to wait for almost two years for even a "preclinical" gene-therapy protocol. In the summer and fall of 1988, the first gene-marking study was reviewed and approved by the working group and the parent committee. Finally, in 1990, two gene-therapy studies were reviewed and approved. On September 14, 1990, the first officially-sanctioned gene-therapy study began when W. French Anderson, R. Michael Blaese, and their colleagues administered genetically-modified T-cells to a four-year-old girl named Ashanti DeSilva.

In its guideline-writing efforts and its review of the earliest preclinical and clinical protocols the RAC was supported by a series of excellent NIH staff people in an office called the Office of Recombinant DNA Activities (ORDA). The professionalism of this staff, its commitment to the public health and the protection of human subjects, and the long tenure of many of its members have all contributed significantly to any success that the RAC may have had in its oversight responsibilities over the years.

The Years 1991 to 1995: Parallel Efforts by the NIH and the FDA

Gene-therapy research "took off" between 1991 and 1995, and the RAC was hardpressed to review the many protocols that it received, especially during the latter years. In preparation for its June 1995 RAC meeting, RAC members and the ORDA staff undertook a comprehensive review of gene-therapy and gene-marking studies that had been reviewed and approved to date. This review, which was pub-

lished in Human Gene Therapy on September 10th, 1996,[2] revealed that during the first four years of intensive gene-therapy research there were hints of benefit in several studies but that in no case had a patient been cured of his or her disease by this new experimental approach.

In the early 1990s the Food and Drug Administration also greatly enhanced its capability to review Investigational New Drug (IND) applications that employed genetherapy techniques.[3] FDA officials and reviewers regularly attended RAC meetings and increasingly participated in RAC discussions. Researchers began to note differences in the kinds of information being sought by the RAC and the FDA, and some researchers also complained that they had to jump over two regulatory hurdles rather than one.

In response to these complaints and similar complaints by some AIDS activists and biotechnology companies, the NIH and the FDA sought, in 1994, to work out a system of dual submission of protocols and coordinated review. In retrospect, it seems quite clear that this well-meaning effort did not go far enough and that serious differences in emphasis and approach remained between the NIH and its advisory committee, the RAC, on the one hand, and the FDA, on the other. The two agencies also failed to agree on how to develop a data-management system for gene-therapy research.

September 1995 and December 1995: the Verma Committee Report and the Orkin-Motulsky Committee Report

In September 1995 a committee chaired by Inder Verma submitted recommendations to NIH Director Harold Varmus regarding the appropriate role of the RAC in the review of gene-therapy research. The committee concluded that the RAC had an important ongoing role in the review of such research but recommended that the RAC publicly review only research protocols that raised novel questions, for example, protocols that employed a new vector or sought to treat a new disease. For all other protocols, those that did not raise novel questions, the Verma Committee recommended that the review be conducted solely by the FDA.

In December 1995 a committee chaired by Stuart Orkin and Arno Motulsky delivered a somber verdict on the first five years of publicly-reviewed and -approved gene-therapy research, Not a single, study had demonstrated clinical benefit to patients from gene therapy alone. The committee recommended that more attention be paid to the infrastructure for gene-therapy research, including the development of better vectors and of a better understanding of human immunology.

Eighteen Months of Uncertainty: May 1996 to October 1997

In May of 1996 NIH Director Harold Varmus announced his intention to abolish the RAC in a speech delivered in Hilton Head, South Carolina. This proposal was formulated more precisely in a Federal Register notice published in July 1996. Over the next year and a quarter the RAC's future role was debated by academic people, patient advocacy groups, biotechnology companies, several members of Congress, and RAC members themselves. Two general revisions of the original plan were published in the Federal Register, the first in November 1996 and the second in February 1997. Finally, on October 31, 1997, a new oversight system for gene-therapy research was formally announced in the Federal Register. According to this final plan, the RAC and the NIH would no longer approve or disapprove gene-therapy research protocols. Instead, the RAC would discuss protocols that raised novel issues and make suggestions to the authors of the protocols. It was understood by all that RAC discussions would also inform FDA reviewers in their confidential negotiations with the sponsors of gene therapy research who had submitted the same protocols as part of the IND review process.

There are five other features of the October 1997 plan that are worthy of note. First, the Office of Recombinant DNA Activities accepted responsibility for developing a data-management system to assist the RAC in its review of adverse events and its annual audit of gene-therapy research. Second, gene-therapy researchers had a clearly-stated duty to inform ORDA and the RAC of any changes in RAC-reviewed protocols that occurred between the time of RAC review and time that the researchers received permission from FDA to proceed with their proposed research (under an IND). Third, gene-therapy researchers also had a clearly-stated duty to report "any serious adverse event" in a gene-therapy research protocol to ORDA.

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[2] Gail Ross, et al., "Gene Therapy in the United States: A Five-Year Status Report," Human Gene Therapy 7(14): 1781–1790; 10 September 1996.

[3] See the FDA's "Points to Consider" document, published in 1991 by the Center for Biologics Evaluation and Research and entitled "Point to Consider in Human Somatic Cell Therapy and Gene Therapy." See also David A. Kessler, et al., "Regulation of Somatic-Cell Therapy and Gene Therapy by the Food and Drug Administration," New England Journal of Medicine 329(16): 1169–1173; 14 October 1993.

Fourth, researchers were required to submit Annual Data Reports to ORDA for inclusion in the data-management system and analysis by the RAC. Finally, ORDA and the RAC would plan Gene Therapy Policy Conferences to look at broad themes like genetic enhancement, in utero gene therapy, or the use of lentiviruses as vectors.

From October 1997 to the Present: How Is the New System Working?

There is some good news to report from the past two-plus years. The Gene Therapy Policy Conferences have been highly successful in promoting interdisciplinary discussion of several important topics. RAC members continue to be deeply committed to their public roles and have been quite forthright in expressing concern about being asked to treat adverse-event reports as proprietary information. Similarly, the staff people at ORDA (recently made a part of the NIH Office of Biotechnology Activities [OBA]), have devoted long hours to fulfilling the roles assigned to them under the October 1997 agreement.

However, a series of developments from September 1997 through January 2000 have made it clear that there are serious problems in the current oversight system for gene-therapy research. My goal in enumerating these problems is not primarily to blame any individual or group of individuals, but rather to provide evidence that the oversight system as a whole is failing.

First, the data-management system, discussed and planned for since 1994, is still not available. This system is essential for the timely reporting and analysis of adverse events and for the RAC's annual review of gene-therapy research. Initially, delays occurred because of FDA's 1995 decision not to collaborate in the development of the database. In recent years ORDA has not had sufficient staff or resources to complete the development of the database.

Second, many gene-therapy researchers who are covered by the NIH "Guidelines for Research Involving Recombinant DNA Research" have either been oblivious to their responsibility to immediately report serious adverse events to ORDA (and thus to the RAC) or have neglected to fulfill that responsibility. The requirement is not new. It has been included in the RAC's "Points to Consider," in one form or another, since January of 1985. One of the most disheartening statistics that I have seen during the past four months appeared in a recent letter from former NIH Director Harold Varmus, to Congressman Henry Waxman. According to Dr. Varmus, only 39 (or 5.6 percent) of 691 serious adverse events in gene-therapy research using adenoviral vectors had been reported to ORDA before October 1999, when NIH and FDA began a vigorous joint effort to gather and analyze those events. [4]

Third, the lack of coordination between the NIH and the RAC, on the one hand, and the FDA, on the other, continues in certain arenas. The two parent agencies have had different histories and sometimes reflect those histories in divergent approaches to the same question. Important issues remain unclarified—for example, Is the RAC advisory to FDA, or not? If so, does the RAC provide this advice formally or informally? Certain modes of FDA-NIH cooperation that should have been put in place by October 1997, at the latest, have only been initiated within the past two months, in response to a crisis. Here I am thinking especially of two welcome changes in FDA's standard operating procedures. In December 1999, FDA began reporting weekly to the OBA on changes to gene-therapy research protocols and on adverse-event reports from the preceding week. I cannot understand why these lines of communication were not opened years ago.

Finally, I will express a concern based on reports that I have heard from several usually-reliable sources. It is possible that the FDA itself is not adequately staffed to analyze the serious adverse events emerging from this one area of biologics research, and that its own data-management systems include only a fraction of the adverse-event information that is submitted by the sponsors of gene-therapy research. Thus, I would like to ask the FDA three questions - not in order to criticize but rather in the spirit of working toward a better oversight system : What percentage of the 691 serious adverse events in trials using adenoviral vectors were included in FDA's online databases before October 1999? What fraction of these events had to be retrieved from paper reports? And what fraction had not been reported to FDA at all before the vigorous joint effort of FDA and NIH to track down all such events? Even if all these adverse events were captured in online databases by the end of September 1999, a further question can be raised: Would FDA welcome the creation of an independent Data and Safety Monitoring Board (DSMB) that would also be able to gather, analyze, and act upon reports of adverse events in gene-therapy studies?

A Response and Five Recommendations

[4] Letter dated December 21, 1999, p. 7.

As a nation we can do a better job of protecting the human subjects in gene therapy studies than we have done during the past ten years. The death of a generous young man, the serious side effects experienced by several - and perhaps numerous other subjects, and the almost-total breakdown of the system for reporting serious adverse events to ORDA (OBA) and the RAC should be a wake-up call to us all.

How can we do a better job? In my view, five steps need to be taken.

1. The role of the RAC in the oversight of gene therapy should be strengthened rather than weakened. This public advisory body has a 25-year track record and a national and international reputation for integrity and independence. The RAC is one of the public's best guarantees that gene-therapy studies will be conducted in a way that respects the rights and the welfare of the courageous people who volunteer to participate in these studies. Implicit in my request for strengthening the RAC's role is an appeal to the NIH Director to restore the RAC's authority to approve and disapprove individual gene-therapy research protocols.

2. We should provide the human subjects who participate in gene-therapy research with the same kinds of protection that we provide to other subjects enrolled in multi-center clinical trials. Human subjects in AIDS trials and in the Women's Health Initiative (WHI) clinical trial enjoy the benefit of having Data and Safety Monitoring Boards (DSMBs) review the data emerging from these studies at regular intervals. The DSMBs are in a position to warn both researchers and research subjects if unexpected patterns of adverse events begin to appear.[5] Both the NIH and the FDA have been strongly supportive of the DSMB concept. (In fact, the Heart and Lung Institute at the NIH established the earliest DSMBs in the 1970s.) The Institute of Medicine committee that investigated the deaths of multiple human subjects in the Fialuridine (FIAU) clinical trial also vigorously endorsed the creation of "some form of independent safety monitoring" in clinical trials.[6] My specific suggestion is that the NIH and the RAC should take the lead in establishing a Data and Safety Monitoring Board for all human gene-therapy studies and that RAC members should be included in the membership of this DSMB. The DSMB would then report important findings to the RAC on a regular basis.

3. The staff that supports the RAC should also be substantially increased, so that it can contribute more effectively to high-quality research and patient safety. The RAC staff will need to coordinate the gathering, processing, and timely reporting of adverse event data for the DSMI3 or contract with an existing coordinating center that regularly performs such data collection and analysis.[7,8] In addition, the RAC staff could play a more active role in the design of gene-therapy protocols and the writing of better consent forms if it added staff members who could provide technical assistance to researchers and local Institutional Review Boards.

4. The Office of the Secretary for Health and Human Services should become more deeply involved in the oversight of gene-therapy research. Her office is playing an increasingly important role in all human-subjects research, as evidenced by the move of the Office for Human Research Protections to DHHS[9]. In addition, the Secretary can and should ensure that NIH and FDA cooperate fully in their oversight of gene-therapy research.

5. Finally, the Congress may want to consider where the RAC and its staff should be located within the Executive Branch and, more specifically, whether the RAC should be elevated to the level of DHHS. On this point I will tentatively put forward a fifth and final recommendation: Perhaps the RAC and its staff should become advisory to the Secretary of Health and Human Services (or her designee) rather than to the NIH and less formally—to the FDA. There are three arguments that seem to me to support this proposal. First, as I noted earlier, the regulation of human-subjects research is increasingly focused in the Office of the Secretary rather than at the NIH. Second, the Office of the Secretary may be in a better position (or more willing) to support an expanded RAC staff than the NIH has been. And third, the

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[5] For an excellent discussion of the role of DSMBs, see Lawrence M. Friedman, Curt D. Furberg, and David L. DeMets, Fundamentals of Clinical Trials (3rd ed.; New York: Springer-Verlag, 1998), pp. 345–356, esp. 349–350.

[6] Institute of Medicine, Committee to Review the Fialuridine (FIAU/FIAC) Clinical Trials, Review of the Fialuridine (FIAU) Clinical Trials (Washington, DC: National Academy Press, 1995, p. 13; see also p. 14.

[7] For an eloquent plea for greater openness by both sponsors and the FDA in publicly reporting adverse events in clinical trials, see Institute of Medicine, Review of the Fialuridine (FIAU) Clinical Trials, p. 41.

[8] See Friedman, Furberg, and DeMets, Fundamentals of Clinical Trials, p. 348.

[9] On the rationale for relocating the Office for Human Research Protections from NIH to the Office of the DHHS Secretary, see the "Report to the Advisory Committee to the Director, NIH, from the Office for Protection from Research Risks Panel," June 3, 1999. URL: www.nih.gov/welcome/director/060399b.htm.

RAC's mission differs in important ways from the roles of the NIH and the FDA. The primary role of the NIH is to fund research of excellent quality. The principal roles of the FDA vis-a-vis gene therapy research are to regulate the research in a private and confidential manner and to approve new products. The mission that I envision for an enhanced RAC is to oversee both NIH- and privately-funded research on gene therapy, to publicly review and approve or disapprove selected gene-therapy research protocols, to monitor adverse events with the aid of a DSMB, and to keep the public informed about new developments in the field. In my view, this expanded mission for the RAC fits most appropriately with the broad authority of the Secretary for Health and Human Services.

Mr. Chairman and Members of the Subcommittee: The task that we are involved in today is a worthy, indeed a noble task. We are attempting to respond to system failures and the tragic death of an altruistic young man by devising a better plan for overseeing gene-therapy research in the future. If we are committed to doing this job well, I am convinced that we can create a new model for protecting the human subjects who make this research possible. If this model succeeds, public confidence in gene-therapy research will be restored, and the great promise of this important area of research will, I believe, begin to be realized. If the model succeeds, we will also have made an important contribution to the future of biomedical research. When the next major biomedical technology emerges (it may be xenotransplantation), we will be poised to oversee its development in a more effective and a more respectful manner.

Senator FRIST. Mr. Parker.

Mr. PARKER. Thank you, Senator Frist.

As you said, I am testifying today on behalf of the Biotechnology Industry Organization based in Washington, which represents about 850 companies, academic institutions, State biotechnology centers engaged in very diverse research such as research on medicines, diagnostics, agriculture, pollution control and industrial applications. But I am also very happy to answer questions based on my personal experience in the field.

For example, we are very happy to provide you with a sample of our informed consents that we use for our clinical trials so you can see from a corporate standpoint the types of information that we include.

I very much appreciate the opportunity to participate in this very important discussion related to patient safety and oversight and systems for patient safety.

Before I proceed, I would also like to offer my condolences to Mr. Gelsinger for the loss of his son.

First, I have to say that we in the industry were very, very surprised and very disturbed to read about the recent reports of regulatory violations at the Institute for Gene Therapy at Pennsylvania. If these violations did occur, we definitely believe that this behavior cannot be tolerated and should be penalized. I know for sure that my colleagues in academic and in the industrial groups that I work with share that opinion.

I want to summarize my major points first, in the interest of time. I know you probably have a lot of questions.

My first point would be that gene therapy, as you have heard today, has the great potential to provide treatments to millions of Americans who suffer from genetic diseases and also acquired diseases. This research has to go forward, and we really must continue to regulate it so that it can move forward.

My second point would be that biotechnology companies, companies focused on gene therapy and trying to turn that idea into real drugs very much expect and welcome science-based regulation from the FDA for gene therapy clinical trials as we in the industry do

for all drug development. We feel that the FDA does a good job with this oversight and should remain the primary regulatory body to look at INDs and drug applications.

Compliance with FDA regulations is critical for patient safety, and those not in compliance need to be penalized. We would very much support greater resources allocated to FDA to help them ensure this mission is accomplished if there are issues with that now.

Finally, BIO and the gene therapy companies in BIO very much want to cooperate with the RAC, with the FDA, and with you to ensure that any questions about patient safety are answered. To that end, we have already made a concrete offer to the RAC which would provide it with additional information over and above the information it currently gets and that will allow it to fulfill its role as a body that discusses overriding policy, safety, and ethical questions related to new technology. This proposal is attached to my full testimony, so I will not read the entire proposal now.

There has been tremendous excitement about the prospect of finally knowing all the genes that make up the human being. But in order to turn the information from the genome projects into real products, gene therapy is going to play a very big role. Gene therapy allows us to really put that knowledge to work. We think that for patients with some of the 5,000 genetic diseases and many other acquired diseases, gene therapy finally offers hope that these diseases can be efficiently controlled or cured.

My company, Targeted Genetics, has been in existence since 1992. We are currently developing a number of products in clinical studies for the treatment of cystic fibrosis and cancer, products that are in Phase I and II trials currently, products that could be in pivotal trials in the year 2001. So we and others in the industry are starting to see a glimmer of the promise of the fulfillment of this whole idea of gene therapy reality, and we are very excited about that.

Let me turn to the regulatory and oversight system changes that we and others have proposed. First, I want to say that it has been reported in the media that the biotechnology industry and the gene therapy companies that sponsor clinical trials are seeking to reduce the level of Federal oversight in this field. That is simply and absolutely not true, and I want to be clear about this position.

BIO welcomes and expects strict, science-based oversight of our research and development activities by the FDA, and in fact, commercial acceptance of our products depends on our ability to show that these products have met rigorous testing criteria, as is the case for all therapeutic products and all products regulated by the FDA.

Moreover, our industry very much welcomes a public discussion about the ethical and social implications of specific applications of biotechnology. Toward that end, the guidance and input from interactions with the RAC has been very, very critical for our sector. We believe that the regulatory body governing individual human clinical trials, the FDA, does a very effective job of overseeing patient safety. There may be a resource question there, though, and I will again reiterate that we welcome and would lobby for more resources for the FDA.

Personally, I and others in the industry have been very impressed with the scientific expertise and caliber of FDA reviewers with whom we have interacted, and I think it is very important to remember that the development process for turning a gene into a therapeutic product carries with it the same sort of stringent requirements and testing standards as those for any other therapeutic product. Due to its knowledge of the drug development process, FDA is well-suited to the task of overseeing trials involving individual gene therapy products.

Industry takes its compliance with FDA regulatory requirements extremely seriously. It is not only a legal requirement and ethical imperative, but also an essential business practice to comply wit hall FDA regulations at all times. For example, even the receipt of a simple warning letter can so damage a company's credibility that its products are not accepted, its stock may fall dramatically, and its financial and commercial development partners and potential partners may walk away. So that while patient safety is our ultimate first goal, it is very important from a business standpoint as well to comply with FDA regulations and to ensure that all compliance issues are met.

In November of last year, as you know, the NIH proposed an expanded review system related to adverse events in gene therapy trials, and while it was a very good effort, many members of the committee itself had some issues with the proposal as to whether or not it was feasible.

BIO has proposed an alternative approach for the reporting of adverse event data to the RAC by sponsors. This proposal is designed to provide the maximum safety information without compromising patient confidentiality. And again let me be clear—under the BIO proposal the RAC would receive reports of adverse events from company sponsors in addition to the investigator requirements as currently written. So this would be insurance that the information is getting to the RAC in an appropriate way.

Again, in the interest of time, I will not go through all the details of this proposal but will just say that it would involve a harmonization of requirements for sending SAE reports to both the RAC and the FDA; very much a continuation of the respective roles of the two agencies. FDA would remain the only agency with regulatory authority and the ability to approve a trial or put it on hold, but the RAC would very much maintain its role as an educational advisory body and an arm for getting public information out so these issues can be dealt with.

We would like to see an agreement between industry and the NIH that would just memorialize how the data would be used, and we believe the OBA would be responsible for developing a mechanism to ensure that patient confidentiality is protected and that commercial development information remains confidential.

In conclusion, the organizations represented by BIO remain fully committed to providing the resources necessary to fully realize the promise of gene therapy for the treatment of a number of diseases. We think it is very vital that patients with these conditions have access to novel therapies, and we believe that existing FDA and NIH rules provide strong safety oversight for gene therapy prod-

ucts if all groups testing gene therapy products comply with the regulations.

We are very happy to work with the RAC and with you and with the FDA to make sure that these issues are dealt with, and we will do what we need to do to help in this matter.

Thank you very much.

[The prepared statement of Mr. Parker follows:]

PREPARED STATEMENT OF STEWART PARKER

Good morning. I am Stewart Parker, CEO of Targeted Genetics Corporation, a biotechnology company based in Seattle, Washington. I am testifying on behalf of the Biotechnology Industry Organization (BIO), which represents 850 companies, academic institutions and state biotechnology centers engaged in biotechnology research on medicines, diagnostics, agriculture, pollution control and industrial applications.

I very much appreciate the opportunity to participate in this discussion related to oversight of gene therapy.

Before I proceed, I would like to again express my sympathy to the family of Jesse Gelsinger, for the loss of their son and family member. I can only imagine the pain they have endured.

UNIVERSITY OF PENNSYLVANIA CLINICAL TRIAL

We in the industry were surprised and deeply disturbed to read recent reports of regulatory violations at the Institute of Human Gene Therapy at the University of Pennsylvania. These violations have led to the FDA halting all gene therapy trials underway there. If these violations occurred, this behavior absolutely cannot be tolerated, and penalties should be imposed to the full extent of the law. I am certain that my colleagues in the industry, as well as in gene therapy academia agree with me.

OVERVIEW

As all entreprenerus must do, I want to get right to the bottom line:

- Gene therapy has great potential to provide treatments to the millions of Americans who suffer from genetic diseases. This research must go forward.
- Biotechnology companies expect and welcome science-based regulation from the FDA for gene therapy clinical trials, as we do for all other drug development.
- BIO has made a concrete offer to the RAC that will provide it with the information necessary to fulfill its role as a body that discusses overriding policy and ethical questions related to new technology. This proposal is attached.

GENE THERAPY'S PROMISE

I would like to discuss gene therapy, a field that has great potential to provide treatments for both acquired and inherited diseases. The field of gene therapy is focused on finding ways to introduce genes into cells in order to correct a cell malfunction, to add a new function to a cell, or, in the case of cancer, to add a gene to a cancer cell that causes that cell to die. A variety of different types of gene delivery systems are used to deliver genes into target cells. Some systems are made from modified viruses, which appear to be very efficient at getting genetic information into cells. There are many different types of viral based systems, each of which has its own characteristics and safety profile. Nonviral, or synthetic gene delivery systems are also used, each of which, again, has its own unique profile. The goal is to match the appropriate delivery system with the gene, the target cell and the disease, in order to develop effective therapeutics.

There has been tremendous excitement about the prospects of finally knowing all the genes that make up the human being. Gene therapy allows us to actually put that knowledge to work, by creating products out of these genes. There are about 5000 genetic diseases including hemophilia, Huntington's disease and cystic fibrosis. For patients with these diseases and others, gene therapy offers hope that finally these diseases can be efficiently controlled or cured.

Recent reports indicate that this hope is well placed. For example, several gene therapy products have demonstrated safety and have begun to demonstrate efficacy in cancer clinical trials. In addition, recent studies in France have shown that infants suffering from Severe Combined Immunodeficiency Disease (SCID) have had their immune systems completely restored by gene therapy.

TARGETED GENETICS

My company, Targeted Genetics, is a gene therapy company formed in 1992 as a spinout of Immunex Corporation. We currently are developing a number of products, in clinical and preclinical trials, for the treatment of cystic fibrosis, cancer,

rheumatoid arthritis, cardiovascular disease, and hemophilia, using both viral and nonviral delivery systems. Phase I and Phase H clinical data from our lead products, tgAAV-CF, for the treatment of cystic fibrosis, and tgdccElA, for the treatment of cancer, while preliminary, are promising. Our first presentation to the NIH Recombinant DNA Advisory Committee (RAC) was in 199 1, and we have had continued and significant interactions with the RAC.

Having been the first employee of Immunex Corporation, in 198 1, 1 have spent the bulk of my biomedical career developing new technologies, and attempting to translate cutting edge science into new therapeutics. I feel I can speak on behalf of an industry that is trying to overcome technical hurdles and develop products in a sound, responsible manner—products that have potential to treat a vast number of diseases.

REGULATORY AND OVERSIGHT SYSTEM CHANGES

While gene therapy research and development must advance to help the millions of Americans who suffer from serious and often fatal diseases, it is imperative that the technology, like all drug therapy, goes forward safely. Consequently, I would like to discuss regulatory oversight of gene therapy, especially the reporting of data from clinical trials. BIO has developed a position paper on this issue, which is available on its website: www.bio.org.

Let me be clear about our position. BIO welcomes and expects strict oversight of our research and development activities by the FDA. Science based oversight by the FDA is both important and welcomed, particularly for new technologies. Indeed, commercial acceptance of our products depends on our ability to show that these products have met rigorous testing criteria, as is the case for all therapeutic products. BIO has consistently lobbied for additional resources for the FDA, so that it can perform its oversight responsibilities even more effectively.

Moreover, our industry welcomes a public discussion about the ethical and social implications of specific applications of biotechnology. Toward that end, the guidance and input from interactions with the RAC have also been important.

We believe that the regulatory body governing individual human clinical trials, the FDA, does a very effective job overseeing patient safety. The industry has been extremely impressed with the scientific expertise and caliber of FDA reviewers with whom we have interacted. I think it is important to remember that the development process for turning a gene into a therapeutic product carries with it the same sorts of stringent requirements and testing standards as those for any other therapeutic product. Due to its knowledge of the drug development process, FDA is well suited to the task of overseeing trials involving individual gene therapy products.

We also believe the RAC is an entity that is effective in organizing public discussion of any overriding policy issues related to gene therapy. The RAC reporting standards, as currently written, provide an effective opportunity for RAC members, and society, to be alerted to any safety and ethics issue that could be encountered. It is my view that compliance by academic researchers with these reporting standards warrants additional review.

Industry takes its compliance with FDA regulatory requirements extremely seriously. Why? For a company, the penalties for noncompliance, as well as the implications of noncompliance with FDA guidelines are so severe that the result could be the end of the company itself Even the receipt of a simple warning letter can so damage a company's credibility that its products are not accepted, its stock may fall dramatically, and its financial and commercial development partners and potential partners may walk away. It is not only a legal requirement and ethical imperative but also an essential business practice to comply with all FDA regulations at all times.

PROPOSALS REGARDING ADVERSE EVENT REPORTING

In November of last year, the NIH proposed an expanded review system related to adverse events in gene therapy trials, designed to improve safety by requesting more safety reports from gene therapy clinical trials. Many observers, including several members of the RAC, were concerned that this proposal was impractical and would not result in increased safety. It is important to remember that federal law already requires that companies sponsoring clinical trials for gene therapy, as well as other drugs, provide comprehensive adverse event reports to the FDA. Therefore, the only issue here is whether these same reports should be submitted to an additional entity, the RAC.

BIO proposed an alternative approach for reporting of adverse event data to the RAC by sponsors. This proposal is designed to provide the maximum safety information without compromising patient confidentiality or a company's legitimate proprietary data. Under the BIO proposal, the RAC would receive reports of adverse events from company sponsors in addition to the reports it receives from investiga-

tors. The B10 plan would provide this information to the RAC as well as to the FDA.

Our proposal has been agreed to by all the members of BIO engaged in gene therapy research. The proposal sets a new high standard that all these companies must meet. This proposal will substantially increase the data that will be transmitted to the RAC. We believe that this will effectively reassure patients and the public regarding the safety and efficacy of gene therapy clinical trials, enhance the ability of researchers to enroll patients in these trials, and enhance the RAC's role in the process. At the same time, it is consistent with the industry's FDA obligations and confidentiality rules.

Let me be clear. Under the BIO plan, the RAC would receive company reports on safety in addition to the investigator reports the RAC already receives under current reporting guidelines.

There are three likely scenarios to be addressed: (1) research that is industry funded and not taking place at an NIH-funded institution; (2) research that is industry funded but is taking place at an NIH-funded institution; and (3) research funded by NIH with or without industry involvement.

Current law, as codified in 21 CFR 312, imposes reporting requirements on companies sponsoring clinical trials including gene therapy trials. These reports allow the FDA to monitor trials and alert agency officials to possible risks to patients. It is settled law through court decisions and reaffirmations by Congress—that these reports, which may contain data that may identify individuals participating in the trial and competitive commercial information, are kept confidential by the FDA.

This is how our plan would work in these three situations:

Scenario 1: The reporting rules for companies we propose and describe below would apply. The RAC would receive adverse event reports from companies in harmonization with FDA requirements.

Scenarios 2 and 3: In these scenarios, the existing NIH reporting guidelines for academic investigators would apply. In addition, as described in our proposal, companies would provide adverse event reports to the RAC that are currently only provided to the FDA.

Therefore, in any scenario, the RAC would receive data about gene therapy clinical trials.

BIO Recommendations for Gene Therapy Oversight

Specifically, BIO companies propose the following structure for the future oversight of gene therapy:

Sponsoring companies agree to voluntarily provide serious, related and unexpected adverse event reports (serious adverse events or SAEs) that are currently sent on an expedited basis to the FDA to the NHVOBA. Sponsors would also send to RAC the safety data summarized in the IND annual progress report currently only provided to FDA. hi this way, OBA and the RAC would have access to adverse event reports simultaneously with the FDA.

Thus, within the current scope of NIH guidelines, the RAC should adopt safety reporting guidelines that harmonize with the IND reporting rules and format outlined in 21 CFR 312 and current international standards. This process ensures that federal officials have the information they need to make a timely determination about the progress of a trial and whether patients' safety is in danger. In addition, it protects patients' privacy rights and

maintains the integrity of the drug development process.

According to federal regulations, sponsors of clinical trials are required to notify FDA and all participating investigators of any "serious" and "unexpected" adverse event associated with the use of the drug being tested in the clinical trial within 7 days of notification of the event if the event was fatal or life-threatening, or 15 days for other serious and unexpected associated events. This information is kept confidential to protect patients' privacy and to protect a sponsor's proprietary data. This process ensures that federal regulators have the information they need to make a timely determination about the progress of a trial and whether patients are in danger and ensures that participating investigators are aware of important safety information. SAEs that are unrelated to the intervention are reported to FDA as part of the annual IND report submitted by sponsors because there is no imminent safety risk. This reporting structure is applicable to the development process for all drugs and biologics.

Coordinating the procedures of the FDA and NIH will also help ensure a discussion between the two agencies as they interpret the data. It is essential that the review and interpretation of submitted safety data be coordinated between FDA and NIH to ensure a single, agreed-upon interpretation of those data. The results of these deliberations could form the basis of public discussion at the RAC meeting. Prior to any presentation of the conclusions from this assessment, however, the

sponsor should be made aware of the findings, and have the opportunity to provide additional information or comment. Sponsors should also have the opportunity to present data at the RAC meeting.

Although the NIH guidelines and FDA reporting requirements would coincide, the respective roles of the agencies would remain the same. FDA would remain the only agency with regulatory authority and the ability to approve a trial or put a trial on hold. The RAC would maintain its role as an educational advisory body.

Reporting of adverse events to NUVRAC in addition to FDA is only acceptable to BIO in the case of gene therapy because of the established role that NIH has to oversee novel human gene therapy experiments.

The industry's willingness to provide adverse event data to the RAC is contingent upon an agreement between NIH and industry that would memorialize how the data will be used. OBA would be responsible for developing a mechanism to ensure that patient privacy rights are protected and that commercial development information remains confidential. How will the agency carry out that mission? What patient data will become public? How will the RAC ensure that confidential commercial and financial information from companies will not be disclosed in some untimely or wholly inappropriate manner? How will the RAC use this data to complement the oversight role of the FDA? We call upon the OBA to develop a proposal that would answer these questions and we offer any and all assistance they may require.

These issues should be resolved for investigator-reported data as well. Our concerns about patient confidentiality and the publication of commercial information also apply in these situations.

OBA should work with FDA, industry, and investigators to develop a process that will provide the RAC with adverse event data it needs to do its job effectively, but also will ensure that this information will be used appropriately. The industry stands ready to work with OBA and FDA on this matter. We look forward to this collaboration.

Once the RAC, FDA, and industry agree to a reporting structure, BIO recommends that the process have a life span of one year. At the end of that year, industry will, in consultation with RAC and FDA, evaluate the system to determine if it should continue or if it needs modification.

CONCLUSION

The organizations represented by BIO remain fully committed to providing the resources necessary to fully realize the promise of gene therapy for the treatment of serious medical conditions such as cancer, cardiovascular disease, and genetic and metabolic diseases. It is vital that patients with these conditions have access to novel and innovative therapies. To meet that end, gene therapy research and clinical trials must be regulated in a rigorous but efficient manner, in accordance with clear federal statutes and guidelines.

We believe that existing FDA and NIH rules provide strong safety oversight for gene therapy products. BIO companies are proposing to provide the RAC with additional data under appropriate circumstances. We look forward to working with both FDA and NIH, as well as Senators and Members of Congress on a proposal that will protect patients while promoting gene therapy.

Thank you for the opportunity to provide these comments. I'll be happy to answer any questions you have.

Senator JEFFORDS [presiding]. Thank you very much, Ms. Parker. We have heard today that patients need to know more about research trials that they are recruited to participate in. Could you elaborate on the steps that the private sector takes to ensure patient understanding as to risk and their safety? What would happen to industry employees who fail to abide by the FDA or NIH requirements? What are you doing to really ensure the safety of the individuals who participate?

Mr. PARKER. Certainly, Senator Jeffords. I would say first, speaking from my experience, that before we initiate a Phase I clinical trial, we have staffers who are clinical research associates and regulatory associates who go to our respective academic centers where our studies are conducted, they sit down with the clinical investigators and with their staffers, they review all the paperwork for the studies, they review all the informed consent information as well as the patient eligibility criteria to make sure that the i's are dot-

ted and the t's are crossed. Again, from a company standpoint, if we are penalized by the FDA, it is very serious, so we take those responsibilities very seriously, and I think we provide an extra layer of compliance in that regard.

Senator JEFFORDS. Dr. Walters, I understand the unique opportunities that gene transfer presents. However, when FDA determines a trial is safe, why do we need NIH and the RAC to duplicate the Government's efforts?

Mr. WALTERS. Here, I think there are complementary roles that the FDA and other bodies can play. By statute and by regulation, FDA has to conduct most of its business in secret. In my view, the public needs to be kept abreast of what is happening in this important field of research.

Also, the Data and Safety Monitoring Board that I have suggested would be able to gather and provide cumulative information on adverse events over multiple trials, look for patterns, and might be able to provide the kind of early warning system which did not occur in the case of adenoviral vectors.

Senator JEFFORDS. Please elaborate on why gene transfer clinical trials should be treated differently from trials in other biological areas.

Mr. WALTERS. I think there are certain areas of biomedical research that deserve especially careful oversight in the early years of their development. There was a lot of debate about whether human gene therapy should be performed at all in the seventies and eighties, and we came to a social consensus that it would be all right, but under special oversight rules.

At the present time, we have xenotransplantation, the transplantation of animal organs or cells or tissues into humans. That again raises a variety of questions and may require special scrutiny for a few years at the beginning of its development. If the field becomes safe, if the new therapy becomes effective, then I think the need for special and enhanced oversight goes away, and it can be regulated on a routine basis by the FDA.

Senator JEFFORDS. Dr. Verma, can you describe how the academic research community differs from the procedures described by Ms. Parker?

Mr. VERMA. I do not think the academic community differs from the procedures overall described by Ms. Parker. The academic community, when they get involved in clinical research, must go through very similar procedures. They have to go through the RAC, and then they have to go to the FDA, and the FDA has the final authority of approval whether to conduct the trial or not. So the procedures are essentially the same.

Senator JEFFORDS. When sanctions apply to academic researchers who fail to comply with FDA and NIH rules, what happens?

Mr. VERMA. This is the first instance I know of where it has been brought out that there are failures of rules, at least publicly acknowledged. Clearly, again, the FDA has come out with a number of violations against academic institutions where the trials were conducted. I will refrain from my own judgment because I have not yet seen the rebuttal from the University of Pennsylvania scientists and how they will respond, but the general notion is there that if violations of accepted procedures have occurred, there should be

consequences and penalties, and whether they are academic researchers or whether they are industrial researchers, I think should make no difference whatsoever.

Senator JEFFORDS. Ms. Parker, you mentioned that the industry and your company have informed consent forms that you will share with us. What type of information do you believe should be shared with patients?

Ms. PARKER. Well, I agree very much with the gist of the conversation that we have heard today from the patients. I think we need as much information about past experience with the drug, what has been seen in all the animal studies, what has been seen in the human studies to date. These and the drug safety brochures are updated on an ongoing basis, so I think we cannot mislead patients and let them think there may be cures in these particular trials, if they are Phase I trials, for example. Phase I trials are meant to look at safety; we are not looking at efficacy. So, speaking for the industry and speaking for myself, I am very much in alignment with what has been discussed, that we need to have full disclosure of all events that have occurred with the drug to the patients.

I want to thank you all. We have a vote on, so I will have to run over and vote now, but Senator Frist will return.

I want to thank all of you for your testimony this morning. It has been very moving, and these are very serious consequences that we have been discussing. I want to thank you for enlightening us to make sure we do not do anything to interfere with proper research and that we have the proper protections for those who are involved.

Thank you all. Dr. Frist will be back shortly.

[Recess.]

Senator FRIST. I apologize for the vote. We are in a series of votes now, thus I will keep my questioning short. In response, I ask you to keep your remarks fairly tight.

Ms. Parker and Dr. Walters, the issue of financial incentives in clinical trials, has been raised. Some investigators do have a financial interest in terms of a potential product, which could lead to an obvious conflict of interest.

How do you suggest that we systematically, in a reasonable way, deal with this potential problem? Let me start with the two of you, and then Dr. Verma can comment as well.

Mr. Parker. This has been a difficult issue for the drug, pharmaceutical, biotechnology industry in general, and many people smarter than I have tried to deal with it. The consensus seems to be around complete and full disclosure related to any researcher who does have a financial interest.

Beyond that, it seems that many institutions now are saying that if you are involved in a clinical trial, you cannot hold an equity interest in the company that is conducting the trial.

But I think you have also heard that many of these trials—and the trial that is the subject of this discussion today was not related to a corporation but was purely an academic study. So obviously, there are issues beyond this particular financial conflict of interest that need to be looked at.

Senator FRIST. Dr. Walters.

Mr. WALTERS. First of all, any financial interest of any researcher has to be disclosed to the patients both orally and in the written consent form.

Senator FRIST. What do you mean it has to be?

Mr. WALTERS. From a moral point of view, it just needs to be disclosed.

Senator FRIST. Do you think it is today?

Mr. WALTERS. I do not know what the practice of institutions is. It is not part of the rules that regulate human subject research; it is not part of the Federal rules.

In addition, following up on something that Mr. Gelsinger said, I think it is very important that patients have someone to whom they can go for an expert consultation on whether it is in their best interest to take part in a clinical trial.

Senator FRIST. And is that a part of any clinical trial today?

Mr. WALTERS. Any clinical trial. Ideally, that would be one's primary care physician, but much of gene therapy is so complex that we may have to figure out new mechanisms for helping people to get unbiased information about a gene therapy trial before they decide whether to go in.

Senator FRIST. If our goal is fully-informed patient consent, viewed from an ethical standpoint with regard to financial interest, should we have full disclosure at this point?

Mr. WALTERS. Absolutely full disclosure.

Senator FRIST. Dr. Verma, do you have any comment?

Mr. VERMA. I just want to make one quick comment on the fact that the biotechnology industry is relatively young. It does require considerable participation of academic scientists, and I think that is why there is considerable overlap there. But I agree completely with Dr. Walters that there should be complete financial disclosure of it, and I also think there is great merit in Mr. Gelsinger's suggestion of an advocate who can then tell the patient all the details that are required. Most institutions have very stringent rules on it, and that is the way I think most institutions should function.

Senator FRIST. Thank you, Dr. Verma.

It is a young science, it is an exciting science, tremendous from the genetic and nongenetic disease standpoint. Most professional studies, like transplantation, the field that I know and participate in, are a community; these groups meet together; they know each other; they talk about professional approaches and professional ethics. Does the study of gene therapy have a cohesive group of people that have constant meetings? I ask this because I heard the NIH and the FDA claim that they require numerous reporting of adverse events, but the investigators are not giving it to them.

Is there a group of people in your societies where you can talk about reporting, have your own internal code of ethics, which is what being in medicine is all about, and improve the reporting? How tight a society is this?

Mr. VERMA. The American Society of Gene Therapy is also a very young one—this is only its third year—and we have become extremely concerned with this particular event because Dr. Wilson is an extremely respected scientist and is the former president of the American Society of Gene Therapy.

We have our own code of—there have been several discussions among the board members—in fact, yesterday there was a press release completely conforming to many of the things we have heard. In fact, we will have greater participation. We will have educational seminars at our next annual meeting. We will have a special seminar just with the regulatory authorities, asking the question how best can we serve the community, and there will also be a session on financial arrangements and how else—the question that you just raised—we must rise above that.

So in fact the Society is going to be very intimately involved in these things.

Senator FRIST. Dr. Verma, you have heard today about statistics and reporting and inadequate reporting; "noncompliance" is a word we have heard again and again. That is aimed directly at the research community, from what we heard in the second panel. Why have our clinical investigators, our research communities, inadequately responded to what is written in regulation and required by the NIH and the FDA?

Mr. VERMA. I am quite disappointed to hear that they did not respond to it, although—I myself do not do clinical research—it could have been that perhaps the wording was such that they are "expected" to report. I think the wording should have been that they are "required" to report every adverse effect.

Senator FRIST. In 1996, or around that period of time, you were one of the people who said RAC should reorient, and the authorization process should shift. Do you think that that shift that the NIH carried out, and that you agreed with, in some way detracted from the investigators' commitment to reporting that data?

Mr. VERMA. It is hard to really tell what happened now in retrospect. But I chaired the Committee, and Dr. Walters was a participant with me many times, and we came to the conclusion that the FDA had the regulatory authority.

Senator FRIST. Had what?

Mr. VERMA. Had the regulatory authority. If RAC approved something and FDA did not approve, the clinical trial was not done. IF RAC did not approve something and FDA approved, they could still have gone ahead with the clinical trial. So we felt the best was for RAC to collect data, disseminate information, which was just discussed, and more importantly, conduct policy statements and ask what are the new vectors, what are their dangers, and how can we minimize them. So it was more in that realm that the RAC was to be reconstituted.

Senator FRIST. Why did clinical investigators inadequately report adverse data?

Mr. VERMA. I think there are two points to mention here. One, in the case of gene therapy, "adverse effects" is not necessarily clear. Is it adverse effects due to gene transfer or due to the disease itself? To date, at least as far as the reported ones, we only know the sad death of Jesse as the only one where you have direct involvement of the vector in terms of the disease, and even there, to this date, we do not know why Jesse died and not the other patient who received the same dose. We also do not know what actually caused his death. We have ideas, but we really do not have proof of that fully as yet.

Senator FRIST. Do the investigators not know what an adverse reaction is or what the definition at NIH and FDA is?

Mr. VERMA. I think they should know what an adverse effect is. There is a clear definition of adverse effect.

Senator FRIST. But they are not reporting it, don't you agree?

Mr. VERMA. I heard that today, that they are not reporting; yes.

Senator FRIST. Your societies need to help us figure out why that is the case, because it is not clear to me after sitting here for 3½ hours listening, and I know it is not clear to you either, why for some reason this is not working.

Dr. Walters, Ms. Parker, do you have any comment on reporting? I know we have already discussed it in detail, but it is critical.

Mr. WALTERS. I do have a comment on that.

Senator FRIST. Yes, sir.

Mr. WALTERS. I think the researchers got very mixed messages about the role of the RAC in 1996 and 1997. And there was a period of time when it seemed as if the RAC would be abolished and replaced by a group with a different name and much lower status. And when the RAC lost its approval and disapproval authority, I think one of the unintended effects of that change was that researchers no longer took the RAC as seriously as they had in the past. And when I see compliance rates in the range of 5 to 6 percent, something is radically wrong.

Senator FRIST. You can tell that is my suspicion as well. Now we need to figure out the answer to that, and you have come back with your recommendations on strengthening NIH and RAC as we go forward with the monitoring board.

Ms. Parker, do you have any comment on that? You are on the front line.

Ms. Parker. From my standpoint, I do not really understand why that occurred, either. I am comforted by the fact that it sounds like the FDA was receiving the majority of these reports—I believe Jay Siegel said 95 percent were evaluating the reports. Personally, my company does not work with adenoviral vectors, so I could not really comment on that.

Senator FRIST. How many clinical trials does your company have ongoing?

Mr. Parker. Well, we have two products right now in clinical trials. We have conducted a series of trials earlier in our existence and have actually been conducting trials and been in front of the RAC since 1991.

Senator FRIST. Coming back to the issue of informed consent. Are patients being adequately informed, truthfully and fully today, the way the system is working in terms of their participation in gene therapy trials?

Dr. Verma.

Mr. VERMA. From what I heard from Mr. Gelsinger today, obviously, it was not done right. I think it is essential—it is essential to build the trust of the public and to have the respect of the community. We must give the best possible informed consent to the patient. All details must be given. The safety of it, the likely success of it, the financial arrangements—all of those things must be given to the patient.

Senator FRIST. Dr. Walters.

Mr. WALTERS. I am afraid that this is a systemwide problem in human subjects research and not unique to gene therapy research. There have been several reports, one by the Office of the Inspector General for the Department of Health and Human Services, a GAO report, hearings before both Houses of the Congress, scholarly articles. The problem of tending to overpromise, especially in Phase I studies, in clinical trials is a very broad and serious problem, and we have got to find better ways to get a handle on the problem and give the local institutional review boards the help that they need.

Senator FRIST. I agree that it is a much broader problem than just gene therapy, but with the output of the Human Genome Project over the next 2 years, the potential for new therapies is going to grow exponentially, and therefore I want to focus on gene therapy.

We are talking about investigations in human beings, but in truth it is experimentation in human beings. We know that the future is great, but there is no proven therapy today. There are anecdotal successes, but this is experimentation in human beings. I think what is unique about gene therapy, the reason why we are having this hearing and why I feel we should have this hearing, is that it does introduce something different. That is why we have to go back and address all the systems in place. This is different from transplantation and immunology in that you really do depend on human subjects.

Dr. Verma, let me ask you about that. That leap from animal experiments to human experiences in gene therapy. If you look back at the December 7, 1995 report and recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, one of the findings outlined the difficulty in extrapolating from animals to human studies. They concluded, going back to the first panel, with cases like cystic fibrosis, some cancers, AIDS, that animal models do not sufficiently mimic the major manifestations.

Is that one of the challenges that we face today?

Mr. VERMA. You are absolutely right; it does not always, but this is the best we have. I think it is essential to have that kind of preclinical data. It does not necessarily mean that it will actually be transposed onto the human, but that is the best we have. And I think the striving from our community should be to have better model systems, even better model systems than we have.

Cancer is a good example. In many of the model systems we have in cancer, we actually put the tumor in the animal and then show that we can cure it. That is not how human tumors grow. Human tumors do not come by putting tumors back in. So we have to have a better model system.

So I think the community is very sensitive to it; it is just that scientifically, it is not always possible to have the model system that you want. But this is an essential component.

Senator FRIST. Does the leap to gene therapy studies from animal to human models mean that we by necessity have to accept a greater element of risk than in other traditional medical science and medical fields?

Mr. VERMA. I am not totally familiar with all other medical practices, not being a clinician, but I think there is a certain degree of risk. We have to accept the fact that if it has worked in a mouse

model system, for example, or on a dog model system, and then you go to the human, the best extrapolation you can do is on the basis of those model systems. That is what we have at the moment. So there is a greater risk from that point of view.

Senator FRIST. Let me give each of you a minute or so if you would like—to make any closing statement. I do have a number of other questions, and we will keep the record open so we can continue this dialogue, but let me ask, based on your observations—of today's hearing to make any final remarks.

Mr. VERMA. As I said in my remarks, I think it is a very exciting science. We need to learn from our mistakes to go forward. I think it is essential. Society has a huge stake in science, and scientists will be well-reminded themselves that public confidence and trust is essential for the continuity of scientific endeavors, and in order to do so, we have to abide by the rules and guidelines which we have all agreed to in order to have the public trust restored.

Senator FRIST. Thank you.

Dr. Walters.

Mr. WALTERS. I am optimistic in the long run about gene therapy, and I deeply hope that gene therapy will be successful in the long run in helping to treat and even to cure many human diseases.

I think the field has had a setback in the past 6 months. We knew before that it was not very successful, and now it has injured people. So we need to reappraise, and I think we need to proceed with heightened surveillance of the field and try to find new oversight methods for tracking what is happening with patients who are treated with this experimental approach.

Senator FRIST. Thank you.

Mr. Parker.

Mr. PARKER. I will say that I have now been developing gene therapy products for a long time, and I am very excited. I feel like we are close to so many real effective treatments for diseases that cannot be treated now. The tragic thing is that at the same time, we have had this horrible, horrible incident with the death of Jesse Gelsinger.

So I think the challenge that we all have is to be able to fulfill the promise, to continue to be able to work on these effective therapies and get them through in an appropriate way so that patients who need these treatments are not dying, but at the same time meet the needs of the public and make sure these concerns are answered. We know that sometimes, the word "gene" is sort of a scary word. We need to make sure the public understands what we are doing and appreciates what we are doing and knows the risks involved. In clinical research, there is risk—it is research—but at the same time, it should be informed research. That is what we as an industry group are really willing and able to try to help accomplish.

Senator FRIST. As we set out this morning, in my own mind, I really wanted to be able to answer two questions, and I am partway there. The first question is in this tremendously promising field, are we ensuring that there is adequate protection of human subjects, patients, people, as they participate in this tremendous evolution of science as it goes forward?

I think from what I have heard today that the answer is that we are not doing an adequate job, without pointing fingers, because I think it starts at the very local level and comes all the way to the Federal Government.

The second question that I wanted to answer in my own mind is do the mechanisms that we have in place, the appropriate mechanisms that have evolved over time the RAC, NIH, and FDA are those Government system approaches working to do the following two things; number one, to protect human subjects and number two, to make sure the science is substantial, meaningful, and will produce the outcomes that we all dream for and work toward?

I conclude those systems are not working. They are failing.

Now, we have to decide what to do, where to go, based on what we have learned, based on the testimony from a family who has experienced devastating circumstances and from another individual who has seen benefits to the organizations that are responsible today.

I think this will be the first major commitment by the United States Congress to approach this difficult and complex issue.

The hearing today has been moving; it has been enlightening; it has been very sombering in many ways. We will take the information that we have heard, and we will keep the record open until February 9th for additional comments. The subcommittee will follow up with some additional question to capture some of the things that we did not have time to talk about today.

On behalf of the subcommittee, I want to thank all of our witnesses. We appreciate your taking the time to help better a process that we know is so important to the future of mankind.

[Additional statements and material submitted for the record follows:]

Introgen Therapeutics, Inc.
Written Testimony for the Public Record
Hearing of the Senate Committee on Health, Education, Labor and Pensions
Subcommittee on Public Health
"Gene Therapy: Is There Oversight for Patient Safety?"
February 2, 2000

Introgen Therapeutics, Inc. is submitting this letter to be included as written testimony to be included in the public record for the Hearing of the Senate Committee on Health, Education, Labor, and Pensions Subcommittee on Public Health on Gene Therapy Oversight, held February 2, 2000.

Introgen Therapeutics Inc., a company developing gene therapy products for the treatment of cancer, shares the concerns of the public, Congress, the National Institutes of Health (NIH), and the Food and Drug Administration (FDA) that new drugs be developed responsibly. Introgen Therapeutics would like to respond to three specific issues raised during the hearing. First, that patients are adequately informed. Secondly, those systems in place to regulate clinical studies must be enforced. Third, that some gene therapies have safely demonstrated clinical benefit for patients.

First, Introgen Therapeutics, Inc. believes that the ethical and moral obligation to patient safety in clinical trials is paramount, and that availability of information is integral to achieving informed consent. This requires that patients are made aware of potential risks associated with enrollment in clinical trials and also of what benefits the patient can reasonably be expected to realize. We support the public disclosure of Serious Adverse Events that are associated with the use of the experimental therapy. However, these data should be made public only after they have been placed in appropriate clinical context and patient confidentiality has been ensured. This type of public disclosure will help patients and investigators make a more informed decision when considering the applicability of a clinical trial drug to their individual circumstance.

Introgen believes that informed consent is critically important in the protection of patients and would be happy to provide the Committee with examples of the informed consent documents we use in our gene therapy trials and/or to participate in a discussion of this important issue.

Secondly, Introgen Therapeutics, Inc. recognizes that there is not a functional mechanism to collect adverse event data and make it available to the scientific community. We believe that adverse event reports have been appropriately made to the FDA. Reporting to the NIH "immediately" as mandated by their guidelines, by all organizations engaged in clinical studies has been incomplete. We believe the failure to report adverse events to the NIH are largely due to lack of clear and sufficient instructions to investigators by the NIH. Adverse event reports should be made to both NIH/Recombinant DNA Advisory Committee (RAC) and FDA using a harmonized mechanism. However, there should be a mechanism to force RAC to respond timely and discharge its duties. We can provide examples where RAC has been derelict and apparently not read or distributed information provided by Introgen. Furthermore, the composition of RAC is ill suited to discharge the responsibilities with which is has been charged. We believe reporting should follow the FDA historical guidelines, which are clear, appropriate and enforceable. These guidelines are clearly defined in the US Code of Federal regulations, Title 21, part 312.32 "IND Safety Reports." By contrast, the NIH Guidelines, Appendix M-VII-C "Adverse Event Reporting", are somewhat vague and cross-reference the FDA filing requirement, which we believe may have led many investigators to adopt the standard FDA definitions for adverse event reporting. We strongly believe that regulatory authority should remain with the FDA, as it does with all other clinical testing of experimental therapeutics. The appropriate role of the NIH/RAC is to support the FDA by mobilizing the scientific community for analysis of adverse event trends that pose a potential threat to patients and to educate the public, Congress, and clinical investigators as to

trends in adverse events that must be recognized to ensure patient safety. The White House initiative of February 8th in asking the Secretary of Health and Human Services to intervene in a highly technical, medical and scientific process has politicized ongoing research to discover new therapies that may benefit end-stage patients.

Introgen Therapeutics proposes that the FDA should remain the primary regulatory oversight body for pharmaceutical clinical trials, including gene therapy trials. This body is experienced, apolitical, clearly objective, legally constrained and appropriately trained for this function. Perhaps the policies of regulatory oversight that the FDA has regarding patient safety in clinical trials should be modified. However, it is Introgen's belief that these modifications should encompass an ability to publicly release adverse event data and to initiate inspection audits at an earlier phase of drug development. We believe that the FDA may not have adequate staff to cover the potential increase in the number of clinical trials, related or unrelated to gene therapy, in the near future. We urge Congress to appropriate funding to augment the FDA systems and staffing in place rather than create a duplicative regulatory body.

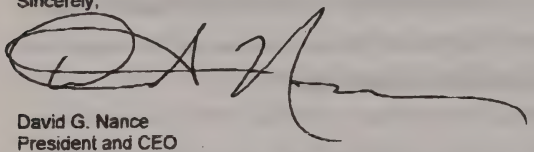
I have been an active proponent for increased funding for NIH research funding. In fact, I personally appeared with Peter Lynch and others before the Congressional Task Force on Science, Healthcare and the Economy in 1998 to emphasize that the future of our technology based economy depends on innovative programs sponsored by NIH funding. I enjoyed interacting with you, Senator Frist, and other senators during that event. However, we emphatically disagree with the testimony of Dr Walters where he proposed increasing the regulatory oversight authority of NIH/RAC. We urge you to sustain efforts of NIH in research, but not allow it to develop into an ill-equipped regulatory body with duplicative oversight function.

Finally, there is clear evidence of the activity of gene therapeutics used in the treatment of cancers and Introgen is initiating pivotal clinical studies to confirm that gene therapy can be beneficial in the treatment of human disease. As exemplified in attached Figures 1 and 2, there is clear clinical activity of Introgen's adenoviral p53 gene therapy, currently in late stage clinical trials for the treatment of cancer. We agree with the opinion of the majority of participants at the Senate hearing on February 2, 2000 that gene therapy trials must continue. We regret the tragic death of Jesse Gelsinger and are disturbed by reports that study protocols were not followed. We

believe that experimental clinical studies require trust between participants, investigators, and regulatory agencies and do not condone any activity that diminishes this trust. Without diminishing the tragic nature of Jesse Gelsinger's death, we remind the Committee that this is the only death that has been clearly associated with experimental therapy in gene therapy trials. We feel it is essential to continue to develop gene therapy as a treatment for human disease along with other new and novel therapeutic approaches. We have safely treated hundreds of patients with thousands of doses of adenoviral p53 gene therapy.

We implore the Committee to not abandon patients who have the right to benefit from gene therapy. It is unethical to delay the development of anti-cancer therapies that are safer than currently available treatments.

Sincerely,



David G. Nance
President and CEO

Introgen Experience with Adenoviral p53 Gene Therapy for Cancer

- 400+ patients treated with thousands of doses administered
- No treatment related deaths observed
- Minimal side effects
- Clear evidence of clinical activity in multiple cancers
- Safety established to satisfaction of FDA in early clinical trials
- FDA reviewed and accepted product registration trials being initiated worldwide
- No maximum tolerated dose (MTD) of treatment reached

Comparative Safety Adenoviral-p53 vs. Standard Therapies for Cancer

- Introgen's gene therapy for cancer is dramatically safer than currently used chemotherapies

Ethical and Moral Obligation to Patients

- New treatments should be made available, without delay, to end-stage patients for whom there are no other alternative medical treatments

Background for Oversight Considerations for Gene Therapy for Cancer

- Regulatory confusion and departmental politics are introducing delays which penalize patients who have limited alternatives
- Patients with acute life-threatening diseases (<1yr survival)
- Most of these patients have no further medical options available to them
- Development of adenovirally delivered gene based cancer therapeutics should continue aggressively
- In cases where a gene therapy has satisfied RAC and FDA safety concerns by progressing to the Phase 3 registration stage, RAC should recognize the ethical imperative to focus on potential patient benefit in acutely life threatening diseases like cancer and not suggest further delay to these pivotal studies

- The RAC should have a limited role regarding products which have progressed beyond Phase 2 clinical development, because safety has been publicly addressed and Phase 3 studies by definition do not introduce a new product class, route of administration, or novel safety issues.

Point 1: Gene Therapy must be regulated, like drug development, but it is impossible to generalize. We must recognize the scope of science and progress achieved in 10 years of gene therapy clinical studies. Drugs developed for different diseases should be regulated differently.

Gene therapy clinical studies now encompass:

1. First time in man studies of novel vectors, but also large, advanced stage studies using vectors that have had extensive public and government scrutiny.

2. Cutting edge science in populations never before subjected to clinical studies, but also common problems such as cancer, where generations of patients have accepted the known and unknowns of clinical studies, and extensive prior regulatory art exists.

3. Single institution studies, but also large multi-national studies requiring complex coordination of multiple regulatory bodies.

4. Early studies that seek to modify the genome, but also studies merely using gene therapy as a means to deliver a drug directly to diseased tissue.

5. Academically driven studies by groups skilled in science, and demonstrably less so in regulatory procedure, but also pharmaceutically driven programs by groups highly skilled in regulatory and clinical trials procedure and precedent.

We need a multifaceted regulatory approach that is keyed to the stage of development of a particular product, not a simplistic one that assumes "all gene therapy is the same" and "everything is equally risky".

Point 2: Duplicative regulatory processes must not delay Phase 3 studies.

Phase 3 studies by definition are built on extensive safety, pharmacokinetic, and efficacy clinical data from Phases 1 and 2.

Phase 1 and Phase 2 data have generally been published and extensively discussed at FDA, and RAC, in the case of gene therapy.

Phase 3 studies represent a lifeline to cancer patients. Early phase studies employ different doses, and comparatively little can be promised to patients; however, Phase 3 studies always use the best dose of agents, and give patients an equal chance of obtaining standard treatment of known efficacy at no cost.

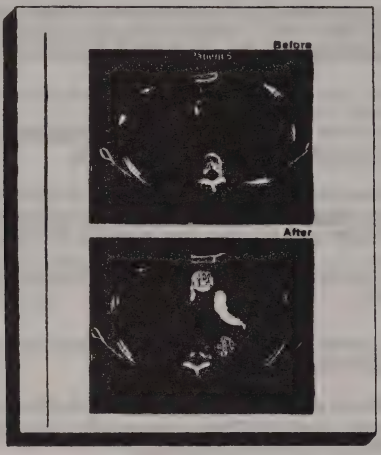
Phase 3 studies, as reviewed and amended by the FDA, represent the best medicine a cancer patient can get for their disease.

We must acknowledge that any unnecessary delay by NIH RAC in initiating a Phase 3 study in cancer is unethical and unconscionable given that FDA has already deemed Introgen's gene therapy safe for a registration study.

Point 3: FDA is the best reviewer of clinical studies for industry.

FDA is the best reviewer of clinical studies for industry because they are not engaged in the development of competing agents and are held to a legal standard of objectivity. RAC, like any body that includes experienced scientists, can have inherent conflicts of interest, and is essentially unregulated. With RAC, the regulated industry lacks an avenue to resolve disputes because no management system exists to override inappropriate committee actions.

Radiographic Response Following RPR/INGN 201 and RT



Before

After

Figure 1

INTROGEN

Radiographic Response Following INGN 201 and RT

Before

After

Figure 2

INTROGEN

UNETHICAL HUMAN EXPERIMENTS IN UNWITTING PATIENTS

Statement For the Record
Submitted To

U.S. Senate Sub-Committee: Public Health & Safety
of the Senate Health, Education, Labor & Pensions Committee
Hearing, February 2, 2000

by

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Citizens for Responsible Care & Research has helped bring to public attention major medical ethics violations in Federally-funded research in which uninformed, vulnerable American citizens are put at high risks without justification. As a result, such individuals have often suffered severe consequences–some have lost their lives unnecessarily. Based on the evidence–including testimonies by families and patients-- we believe five factors contribute to unethical human experiments:

1. Federal regulations are silent about the limits of permissible risk in human experimentation;
2. Failure of Institutional Review Boards (IRBs) to protect human subjects. The entire human research approval process is entrusted to researchers and their colleagues on the IRB. The inherent and documented conflicts of interest preclude their ability to serve the interests of human subjects;
3. The absence of a single Federal authority to guide IRBs and to ensure that human subjects are protected from preventable harm and exploitation; 4. The absence of independent oversight and lack of enforcement of Federal regulations; 5.The absence of accountability when Federal regulations are violated–including informed consent procedures–even when harm results.

Current safeguards to prevent unethical, or scientifically questionable experiments from being conducted on vulnerable Americans-- who are ignorant about the actual risks involved-- are insufficient. In the absence of independent monitoring and oversight, or mandatory reporting of

serious adverse incidents, no authorized agency maintains a record of human casualties of research. This lacuna has given rise to a culture that contradicts medical ethics: it has led some biomedical researchers to put the search for scientific knowledge above the health and welfare of vulnerable, trusting patients, requiring them to assume ever greater risks and potential long-term harm. Jesse Gelsinger was a victim of that culture--and neither the FDA, nor the special NIH Recombitant DNA Advisory Committee (RAC), nor Federal law protected him from this dangerous experiment. Given the risks–such as toxicity and animal deaths in prior experiments–this experiment should not have been approved by the IRB. Even well-meaning researchers need to have limits imposed on the level of risk human subjects are exposed to–they should not be granted rubber stamp approval. Neither Jesse nor other patients like him should have been exposed to unjustifiable high risks.

Evidence indicates that this fatal gene experiment may be the tip of an iceberg. Its value is that the FDA's unusually thorough investigation–after Jesse's death–provides Congress and the public with disturbing, but valuable information ordinarily kept secret. The experiment sheds light on the pitfalls of inadequately regulated human research, demonstrating how the absence of an enforcement mechanism–no advisory committee, under the auspices of NIH (such as RAC), has adequate authority to protect unsuspecting, patients from experiments that cause them needless harm. This experiment clearly demonstrates why we need a National Human Subject Protection Act–with enforcement mechanisms such as are provided under the Animal Welfare Act of 1966. Now more than ever, unsuspecting citizens need to be protected from some overly aggressive researchers whose eyes are on the prize, instead of on the welfare of their human subjects.

Gene therapy experiments are not the only field in which vulnerable patients are exposed to high risks of harm, in speculative experiments with unlikely therapeutic benefits. In a May 4, 1999 letter to the President of the U.S., the National Bioethics Advisory Commission reported:

> "NBAC finds that the absence of Federal jurisdiction over much privately funded research means that the U.S. government cannot know how many Americans currently are subjects in experiments, cannot influence how they have been recruited, cannot ensure that research subjects know and understand the risks they are undertaking, and cannot ascertain whether they have been harmed."

Financial conflicts of interest are rampant and recent findings by the Office of Protection from Research Risks corroborate widespread, outright lawless disregard for medical ethics standards–including Federal informed consent requirements. The Director of the Office from Research Risks acknowledges informed consent violations occur in more than 90% of cases investigated by the agency. Researchers at prestigious academic institutions, the Veterans Affairs Administration, and even at the National Institute of Mental Health fail to comply with Federal regulations, ignoring the safety of vulnerable, often disabled human subjects. Some patients, such as 18 year old Jesse Gelsinger, are not even eligible to participate according to the approved research study protocol, others are dependent mentally disabled and cannot possibly comprehend the consequences of experiments for which they are recruited.

Human subjects' lives are in jeopardy because local Institutional Review Boards (IRB) operate without public scrutiny, thus, they are promoting under major conflicts of interest. Although IRBs are mandated-- according to Federal regulations-- to protect the welfare of human research subjects, financial interests lead them to circumvent ethical requirements that are meant to protect humans subjects from harm. The absence of a single Federal authority to provide oversight and ensure enforcement of Federal standards, has resulted in harmful consequences: IRBs routinely approve research protocols that put patients at risk of serious, often irreversible harm. .

In the field of psychiatric research, we have found evidence demonstrating that neuropsychiatric researchers are putting disabled patients at high risk of relapse and suicide by conducting wholly nontherapeutic experiments, known as chemical "challenge" or "probe." These symptom-provocation experiments are designed to induce severe psychosis and "flash-back" in severely disabled patients–many of whom are recruited in an incoherent, psychotic state in hospital emergency rooms. First, patients in these experiments are subjected to abrupt withdrawal of their prescribed antipsychotic medications ("washout") – thereby causing as many as 40% to 67% to relapse. Then, rather than treating them, researchers further exacerbate their patients' excruciating symptoms with psychosis-inducing controlled substances--chemical "probes" such as: amphetamine, L-dopa, methylphenidate and the PCP-derivative, ketamine,, fenfluramine, among others. Other provocation experiments expose detoxified veterans to addictive controlled drugs such as amphetamine and cocaine. **None of these experiments offer any possible benefit for the subjects, indeed such experiments clearly undermine the welfare of severely disabled patients–including veterans–who seek treatment from doctors whom they perceive as "healers."**

I. A 1995 Yale University experiment conducted at the West Haven VA is described by researchers [Laruelle, et al]. Eighteen stable schizophrenia patients who were living in the community were recruited into an amphetamine experiment . Their medications were abruptly withdrawn ("washout") for at least 21 days–causing three patients to drop out "because of clinical deterioration." The report does not indicate anything about these subjects' welfare. Fifteen remaining patients were then intravenously injected with amphetamine and with radioactive substances.. The risks: "Acute exposure to amphetamine induces emergence or worsening of positive symptoms in schizophrenic patients at doses that do not produce psychotic symptoms in healthy subjects." The experiment "Induced the emergence oor worsening of positive psychotic symptoms" measured by A photo-imaging technique.

II. A 1995 ketamine experiment at the University of Maryland [Tamminga, et al] describes how nine patients responded to the intravenously administered drug, ketamine: " These data suggest that PCP ketamine-induced psychosis closely resembled the patient's own psychotic symptoms... Moreover, these psychotic symptoms were not blocked or reduced by concurrent haloperidol treatment." Furthermore, "several subjects evidenced delayed or prolonged (8–24 hours)psychotomimetic effects such as worsening of psychosis with visual hallucinations...."

The human subjects of these inhumane experiments lack the capacity to evaluate risks and potential consequences. They are especially vulnerable, since their severe mental disability prevents them from functioning independently, limiting their free choice. Therefore, such individuals need added protections for they cannot volunteer freely, or give informed consent for research – as is their human right since the Nuremberg Code. Researchers say "chemical challenge" experiments are a means for studying the underlying pathophysiology of severe mental illness, such as schizophrenia, and that it will lead to improved treatments. In fact, these "fishing expeditions" are often done merely to give researchers an opportunity to use photo-imaging techniques to record brain receptors in action. **Are experiments that undermine the welfare of human subjects morally acceptable?**

NIMH bears the major responsibility for current ethical violations in psychiatric research: As the authorized federal agency approving federal mental health grant proposals involving mentally disabled human subjects and children, NIMH is also entrusted to ensure that government support is provided only if "the rights and safety of participants of clinical research" are protected. But NIMH has been violating its public mandate and contradicting public policy: NIMH has been supporting, conducting, and funding experiments in which human rights are violated, and the welfare of disabled subjects endangered.

The agency's failure to protect "the rights and safety" of disabled research subjects, as is its public responsibility, arises from a fundamental, though undisclosed conflict of interest: NIMH's leading researchers and administrators are members of American College of Neuropsychopharmacology (ACNP), some actually serving on its governing Council. NIMH researchers have formulated lobbying strategies against federal regulatory safeguards. This conflict of interest is reflected in NIMH's January 30, 1998 response to our Freedom of Information requests for Informed Consent documents involving symptom-provoking experiments conducted at, or funded by NIMH: " NIMH is not a repository for informed consent documents; grantee institutions are not routinely required to submit copies of these records in clinical research studies."
Who then, ensures that ethical and legal safeguards are followed and that Informed Consent forms fully disclose the risks involved to comprehending subjects?

Citizens for Responsible Care & Research **Recommends that:**
I **A moratorium on non-therapeutic experiments that put patients at high risk of harm**– such as abrupt drug "washout" and "provocation"experiments that have induced psychotic relapses in patients suffering from incapacitating illness. A moratorium on experiments that expose vulnerable persons to addictive drugs which may, with repeated exposure, lead to addiction and/ or cause brain damage. Such experiments are being conducted on vulnerable, underprivileged persons, including children, who are unable to exercise their rights.
II. **A no-fault personal injury insurance** be required for every human subject of research to cover the duration of the research and one-year following completion. A $250,000 policy per subject (premiums to be paid by the sponsor/ research team/ institutions) would be an incentive to

reduce unnecessary risks and would compensate individuals / family for undue harm. It would also reduce the taxpayers' burden for uninsured persons who may require costly after-care as a result of experimental adverse consequences.

III. **Institutional Review Boards:** at least 51% of IRB members should be **independent scientists and community representatives** not affiliated with the institution. Qualifications for members should include prior training & education in medical ethics and issues related to human subject protections.

IV **Enact A National Human Subject Protection Act** to provide safeguards for **all** human subjects in experimental research to provide regulatory safeguards for vulnerable human beings--at least equal to those currently provided to laboratory animals under the National Animal Welfare Act of 1966. Investigators must be held accountable for the conduct of the research and the well-being of the human subjects.

V. **Establish an independent Federal Review Board** to provide guidance and oversight for research involving vulnerable human subjects–regardless of funding source. The Board should include at least 33% non-scientists to ensure that our public policy and community values are upheld.

VI. **Establish a national data bank for human subject research** in order to facilitate the flow of information and progress, and to avoid unnecessary duplication of efforts, thereby minimizing the use of human subjects in experiments involving more than minimal risks. All physician- researchers should be required to report adverse incidents to this independent oversight board or to the FDA's Physician's Hotline, indicating what preventive measures have been taken to prevent other such incidents.

VII. Require **an independent physician**– not connected with the project-- to monitor vulnerable patient-subjects in experimental research to ensure the subject's well-being, and that continued participation in the research is in the patient's interest. Medical follow-up after-care services should be described, and nature of compensation to those harmed should be stated. NBAC has adopted this position.

FEDERALLY-FUNDED RELAPSE PRODUCING EXPERIMENTS in PSYCHIATRY: DRUG WASHOUT AND CHEMICAL PROVOCATION (a partial list)

National Institute of Mental Health:

* Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, EckelmanWC, and Pickar D: "Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method," *Proceedings National Academy of Science*,1997, 94:2569-74

* Daniel DG; Weinberger DR; Jones DW; Zigun JR; Coppola R; Handel S; Bigelow LB; Goldberg TE; Berman KF; Kleinman JE : " The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia," Journal of Neuroscience, 1991, 11: 1907-1917

* Goldberg TE; Bigelow LB; Weinberger DR; Daniel DG; Kleinman JE: "Cognitive and behavioral effects of the coadministration of dextroamphetamine and haloperidol in schizophrenia," *Amer J Psych* 1991; 148: 78-84

* * Malhotra AK, Pinals DA, Adler CM, Elman I, Clifton A, Pickar D, Breier A: "Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics," *Neuropsychopharm,* 1997, 17:141-50 *Malhotra, A.K, Adler, C. M., Kennison, S.D., Elman, I, Pickar, D, Breier, A: "Clozapine blunts N-Methyl-d-Aspartate antagonist-induced psychosis: a study with Ketamine, " *Biol Psych,* 1997b, 42: 664-668

Brookhaven National Laboratories:

* Volkow ND; Wang GJ; Gatley SJ; Fowler JS; Ding YS; Logan J; Hitzemann R; Angrist B; Lieberman J: "Temporal relationships between the pharmacokinetics of methylphenidate in the human brain and its behavioral and cardiovascular effects." Psychopharmacology (Berl) 199,6 123: 26-33

* Volkow ND; Ding YS; Fowler JS; et al: "Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain," Arch Gen Psychiatry 1995. 52: 456-63

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University of Illinois at Chicago, Department of Psychiatry:

* Sharma RP, Singh V, Janicak PG, Javaid JI, Pandey GN: "The prolactin response to fenfluramine in schizophrenia is associated with negative symptoms," Schizophr Res 1999 Aug 23;39(1):85-9

* Sharma RP; Shapiro LE; Kamath SK; Soll EA; Watanabe MD; Davis JM : "Acute dietary tryptophan depletion: effects on schizophrenic positive and negative symptoms," *Neuropsychobiol* 1997, 35: 5-10

* Sharma RP; Dowd SM; Davis JM; Janicak PG : "Age of illness onset and schizophrenic symptomatology during an inpatient washout period," *Schizophrenia Research,* 1996, 20: 295-300

* Pandey GN; Pandey SC; Dwivedi Y; Sharma RP; Janicak PG; Davis JM: "Platelet serotonin-2A receptors: a potential biological marker for suicidal behavior." Am J Psychiatry 1995 Jun; 152 (6): 850-5

* Sharma, RP, Javaid, JI, Pandey, GN, Jainacak, PG, Davis, JM, "Behavioral and biochemical effects of methylphenidate in schizophrenic and nonschizophrenic patients," *Biological Psych,* 1991,30:459-66

University of Cincinnati College of Medicine:

* Strakowski SM, Sax KW, Setters MJ, Stanton SP, Keck Jr. PE: "Lack of enhanced response to repeated d-amphetamine challenge in first-episode psychosis: implications for a sensitization model of psychosis in humans," *Biological Psychiatry,* 1997, 42: 749-755

Duke University Medical Center

* Mathew RJ, Wilson WH: "Cerebral blood flow responses to inhaled carbon dioxide in schizophrenia," *Acta Psychiatry Scandinavia,* 1990, 81: 497-506

Albert Einstein School of Medicine. Hillside Hospital, Long Island Jewish Medical Center:

* Jody, D, Lieberman, JA, Geisler, S, Szymanski, S, Alvir, JM, "Behavioral response to methyl-phenidate and treatment outcome in first episode schizophrenia," *Psychopharmacol Bull,* 1990, 26:224-30

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* Lieberman JA, Alvir J, et al: "Methylphenidate response, psychopathology and tardive dyskinesia as predictors of relapse in schizophrenia," *Neuropsychopharm,* 1994,11:107-18

Maryland Psychiatric Research Center:

* Buchanan RW; Kirkpatrick B; Summerfelt A; Hanlon TE; Levine J; Carpenter WT Jr: "Clinical predictors of relapse following neuroleptic withdrawal." Biol Psychiatry 1992, 32: 72-8

* Dixon L, Thaker G, Conley R, Ross D, Cascella N, Tamminga C: "Changes in psychopathology and dyskinesia after neuroleptic withdrawal in a double-blind design," *Schizophrenia Research*, 1993, 10: 267-271

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Mount Sinai School of Medicine / Bronx Veterans Affairs Medical Center:

* Davidson, M, Keefe, RSE, Mohs, RC et al., "L-dopa challenge and relapse in schizophrenia," *American Journal of Psychiatry*, 1987, 144: 934-938 *Davidson M, Kahn RS, Powchik P, Wame P, Losonczy MF, Kaminsky R, Apter S, Jaff S, Davis KL: "Changes in plasma homovanillic acid concentrations in schizophrenic patients following neuroleptic discontinuation," *Archives of General Psychiatry*, 1991, 48: 73-76

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NYU Medical Center/ Manhattan Veterans Affairs Medical Center:

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Pittsburgh Veterans Affairs Medical Center:

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* Donovan AM, Halperin JM, Newcorn JH, Sharma V: "Thermal response to serotonergic challenge and aggression in attention deficit hyperactivity disorder children," *Child Adolesc* Psychopharmacol 1999;9:85-91

February 8, 2000

Comments of:
Bill Freese
3206 Shepherd Street
Mt. Rainier, MD 20712

To:
The Subcommittee on Public Health
Committee on Health, Education, Labor and Pensions
United States Senate

RE: Hearing on Gene Therapy Trials, held February 2, 2000 in Senate Dirksen Bldng. 430

Members of the Subcommittee:

I writing to you to express my concerns about the rapidly expanding field of gene therapy. Having followed the press accounts of Jesse Gelsinger's death and the irresponsible conduct of many investigators involved in clinical gene therapy trials, I attended the Feb. 2nd hearing in hopes of finding some answers.

With the exception of Mr. Gelsinger's testimony, however, I was quite disappointed. While some useful information was brought to light, it seemed to me that most of the panel members talked around the important issues. I got the distinct impression that their real purpose was to reassure the public and so prevent a "backlash" against gene therapy rather than protect the safety of future trial subjects.

Senator Frist asked repeatedly why so many adverse events in clinical gene therapy trials have not been properly reported, and never received a good answer. While there are many factors involved here, one very important consideration that was hardly addressed at all in the hearing concerns the financial motivations of the investigators and the sponsors who fund them.

Financial imperatives skew the focus of gene therapy research.

According to Abbey S. Meyers, "the great majority of gene therapy experiments are not conducted on genetic diseases, which are too rare to encourage investment capital, but on cancer, primarily because investors sense that a potential treatment for cancer will be more profitable."[1] This is unfortunate, because genetic diseases – those which involve the absence or mutation of a single or very few genes with little or no environmental influence – clearly offer the most promise of success for this fledgling therapy. Cancer, on the other hand, is an extremely complex disease process that involves multiple genes as well as many environmental factors. Gene therapy experimentation on cancer patients might be compared to the misplaced ambition of a rookie ball player who strikes out every time at bat by attempting to hit home runs rather than slowly honing his skills by swinging for base hits. The home runs will come in time. For now, this misdirected focus probably helps explain the utter failure of gene therapy to achieve any confirmed cures after 10 years of experimentation on thousands of patients.

Corporate funding promotes secrecy and hinders the free flow of vital research findings.

The finding that 652 of 691 adverse events (AEs) in adenovirus gene therapy trials from 1993 to 2000 were not "immediately" reported to the NIH as required by its Guidelines is cause for

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[1] In "A Lot of Rules, Too Many Exceptions," The Washington Post, Outlook, 1/30/00, submitted for the record by LeRoy Walters. Ms. Meyers was a member of the Gene Therapy Subcommittee of RAC from 1989-1992, and a member of the full RAC from 1993-1996.

serious concern. In contrast, investigators seem more willing to report AEs to the FDA. Why the discrepancy? Richard Junghans of the Harvard Medical School and other investigators have claimed ignorance of the NIH reporting requirement. I find this claim totally unconvincing, since the NIH clearly states that all AEs must be reported fully and immediately on every letter of approval sent out to gene therapy researchers.[2] The true reason is that while the FDA keeps AE reports confidential, the NIH shares them with other scientists and the public. Companies that fund gene therapy trials are loathe to divulge any data from trials that might be of use to competitors funding similar experiments. The Biotechnology Industry Association (BIO) goes so far as to claim that details of "adverse events [in gene therapy trials] are, by definition, trade secrets and confidential commercial information."[3]

Since adverse events include deaths, BIO is actually claiming that the circumstances of a trial subject's death is a "trade secret." The perversity of claiming a death or serious illness as confidential commercial information is obvious; yet what makes this claim truly outrageous is that BIO seeks to use commercial property rights to buttress a blatant conflict of interest. No matter how honest or ethical, investigators (and their sponsors) are inclined – by their financial interests, their thirst for fame, pride in their own abilities, and their natural desire to avoid acknowledging culpability for harming a patient – to judge their actions in a favorable light. This is why – until the indisputable case of Jesse Gelsinger – they have unanimously attributed gene therapy trial deaths to the underlying illness and not the therapy itself. It is also why the NIH properly requires that all serious adverse events be reported – so that other, impartial heads might have access to the data and reach conclusions untainted by the personal considerations that will inevitably influence those conducting the experiments.

This is more than a theoretical concern. Three patients in a gene therapy trial conducted by Richard Junghans died under suspicious circumstances that might well have been due to the therapy. Likewise, two patients died in a gene therapy trial conducted by Jeffrey Isner at Tufts University.[4] If the NIH – and hence other knowledgeable scientists working in the field – had been promptly informed of the adverse events surrounding the initial deaths, the combined wisdom of the scientific community could have been brought to bear on the matter, perhaps resulting in modification (or suspension) of the trial and the prevention of further deaths. In the case of Jesse Gelsinger, full disclosure of the results of experiments that preceded his treatment – including the deaths of experimental monkeys and liver toxicity in two human subjects who had received smaller doses of virus than Jesse himself – might have led to modification or suspension of the OTC deficiency trial, which in turn might have prevented Jesse's death.

Eli Giloba of Duke University, who is conducting research in the same field as Junghans, said: "I want to know of any problems other people are having with the same kinds of cells we're using." He adds that NIH's public disclosure of adverse events "is critical for all the clinical investigators who want to do a good job."[5] In short, it is outrageous to permit commercial considerations to choke off the free flow of research findings, which is the only way to protect patients and speed the development of successful gene therapy techniques.

Investigators who stand to profit from their research cannot be trusted to adequately inform potential trial subjects of risks

One of Paul Gelsinger's most damning criticisms concerns the faulty and incomplete information provided to him and his son by Dr. Wilson and colleagues prior to Jesse's trial.

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[2] See "Earlier Gene Test Deaths Not Reported," WP, 1/31/2000.
[3] See "Gene Therapy Firms Resist Publicity," WP, 12/11/99.
[4] See footnote 2.
[5] See footnote 2.

> "He [Jesse] believed after discussions with the representatives from Penn that the worst that could happen in the trial would be he would have flu-like symptoms for a week. He was also told that the most dangerous part of the procedure was to be the catheterization procedure by which the gene therapy would be introduced to his liver and the liver biopsy that was to be done a week later. There was no communication with respect to the danger associated with the receipt of the virus vector gene.
>
> "We were also unaware of the severity of liver injury incurred by several of the patients prior to Jesse. I learned, after Jesse's death, that Penn had removed from the information they gave Jesse and me any reference to deaths of monkeys, which had previously appeared in their documents."

From this testimony, it is clear that Penn representatives substantially understated the risks of the trial to Jesse. They were apparently afraid that full knowledge of the true state of affairs would have caused Jesse and others to refuse to participate. Is this why Wilson's team omitted information about the deaths of monkeys that was in the original informed consent document reviewed by the FDA? Does it explain why they downplayed the severity of liver injury suffered by earlier participants in the trial? Did the Institutional Review Board (IRB) approve the final version of the informed consent document?

These questions should be seen in the context of the funding of University of Pennsylvania's Institute for Human Gene Therapy (IHGT), where the OTC deficiency trials were carried out. IGHT's major corporate backer is Genovo Corp., a for-profit company founded by Dr. Wilson in 1992, and partly owned by the University of Pennsylvania and Dr. Wilson.

> "Under a 1995 deal with Penn, Genovo and its partners, which include four larger biotech companies, have exclusive rights to commercialize gene therapy advances developed at the institute under Wilson."[6]

One of these biotech companies, Biogen, agreed to spend $35 million over five years to help Genovo develop gene therapies to treat lung and liver diseases (e.g. OTC deficiency). Thus, ***both Wilson and the University of Pennsylvania had strong financial interests in ensuring that the OTC deficiency trial went forward***, whatever the risks.

Our concern increases when we learn that scientists and doctors who specialize in genetic disorders, some of whom reviewed the trial for the RAC, raised questions about the study's safety from the outset. Dr. Holmes Morton, an expert in metabolic diseases who runs the Clinic for Special Children in Strasburg, PA, said that there had been enough evidence about the side effects of adenovirus to raise serious doubts about the wisdom of giving it to someone with Jesse's condition.

> "Any time a patient with that disorder is stressed by illness, and in particular any time they develop a fever, their underlying disease becomes not only unstable but life-threatening. That, in a sense, is a quite predictable problem."[7]

Kathryn Zoon, director of FDA's Center for Biologics Evaluation and Research, said that Jesse was ineligible for the trial because his liver function was abnormal when he entered it. Other scientists have questioned the stability of the viral vector used to deliver the gene, the route of

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[6] See "Investor may leave Penn gene therapy group," Philadelphia Inquirer, 1/25/2000.
[7] See "FDA Official Fault Penn Team in Gene Therapy Death," New York Times, 12/9/99.

administration through the hepatic artery, and the high dose given to Jesse, among other dubious aspects of the trial.

When one compares these serious criticisms of the trial with the faulty and incomplete information given Jesse and his father by Wilson's team, it is hard to avoid the conclusion that Dr. Wilson recklessly endangered the life of this 18-year old boy – and was perhaps influenced to do so by motives of personal financial gain.

Financial interests have weakened the regulatory system, particularly informed consent documents

As revealed in the testimony of Amy Patterson, Director of NIH's Office of Biotechnology Activities, the Recombinant DNA Advisory Committee (RAC) has been stripped of its original power to reject gene therapy trial protocols. Now, it serves as merely an advisory body with no real power. Abbey Meyers reports that neither the RAC nor the FDA has the authority to force a change in an inaccurate or misleading informed consent document, and that this authority is vested solely in the local Institutional Review Board (IRB). She adds that: "Members of an IRB (mostly staff of the institution) are usually keenly aware of the need to attract government and industry research grants, and often are unwilling to be too demanding when asked to revise informed consent documents."[8] Now, just when the NIH has discovered over 600 AEs that were improperly reported or unreported, BIO is pushing for still greater relaxation of NIH reporting requirements.

It seems clear that the companies represented by BIO have exerted tremendous influence to weaken federal regulation of their industry. The FDA and RAC – understaffed and with too few resources to adequately review the protocols and oversee the implementation of the many gene therapy trials now underway – have acceded to industry demands for less regulation.

Thus, at a time when medical research at previously independent academic institutions has become increasingly funded and dominated by profit-driven biotech companies, we find a corresponding decline in the extent and quality of federal oversight. One result has been the death of an 18-year old boy who should be leading a happy and healthy life right now. We do not know how many other deaths have resulted from irresponsible investigators left to their own devices by government authorities. How many more deaths will there have to be in the future before decisive action is taken?

RECOMMENDATIONS

1) ***Restrict federal funding of gene therapy to the most promising applications.***

As discussed above, this would be the best means of fostering the troubled field of gene therapy while at the same time protecting patients' safety.

2) ***Bar investigators from conducting clinical gene therapy trials if they have a financial stake in the outcome of the trial***

This is the only way to avoid having investigators placed in the impossible situation of choosing between their personal financial interests and the safety of their test subjects.

3) ***Ensure that all data from clinical gene therapy trials that are in any way relevant to patient safety are made public for peer review***

In particular, reject the position of the Biotechnology Industry Organization that adverse events are "trade secrets" and continue to require reporting of all serious adverse events to NIH's RAC.

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[8] See footnote 1; also see Daniel S. Greenberg, "Our Flimsy Surveillance of Science," WP 1/31/2000.

4) ***Strengthen the review process for clinical gene therapy trial protocols***

In particular, reinstate RAC's authority to review and approve/reject all gene therapy trial protocols. RAC should also be given the authority to review and mandate changes in informed consent documents, given the fact that many Institutional Review Boards lack expertise and are in conflict of interest situations.

5) ***Give the FDA and RAC the funding necessary to conduct more on-site inspections of clinical gene therapy trials.***

6) ***Strengthen enforcement of the NIH Guidelines and FDA regulations relating to gene therapy.***

Irresponsible investigators – especially those with private funding sources – must not be permitted to go unpunished for endangering their trial subjects' safety. Withdrawal of federal funding should be accompanied in more serious cases by suspension of licenses to practice medicine and criminal prosecution.

7) ***Consider legislation to create an independent agency for the oversight of human research subjects***

Rep. Kucinich has introduced legislation to this end.

Sincerely yours,

Bill Freese

UNIVERSITY OF
PENNSYLVANIA
HEALTH SYSTEM

February 4, 2000

Honorable Bill Frist, M.D.
Chair, Subcommittee on Public Health
Committee on Health, Education, Labor and Pensions
United States Senate
424 Dirksen Senate Office Building
Washington, DC 20510-6307

Dear Mr. Chairman,

I would like to take this opportunity to clarify an issue that was raised at the Hearing of the Senate Committee on Health, Education, Labor and Pensions Subcommittee on Public Health entitled "Gene Therapy: Is There Oversight for Patient

Safety?" held Wednesday, February 2, 2000. Senator Hutchinson indicated his understanding that the National Institutes of Health was first made aware of the tragic death of Jesse Gelsinger by reading newspaper accounts. Please allow me to advise you and the other distinguished members of the Subcommittee that this is not, in fact, correct.

In accordance with Federal regulatory oversight requirements, Mr. Philip J. Cross of the Institute for Human Gene Therapy notified Dr. Amy Patterson at the NIH of the adverse event on September 20, 1999, by telephone and via formal letter (Attachments A and B). Please note the widely distributed e-mail letter from the NIH, which expressly commended IHGT for this prompt notification, and stated that its action promoted accountability (Attachment C). Further, as you may know, the FDA was similarly notified of this mournful occurrence at the same time.

Thank you for the opportunity to correct the record on this issue. As President Judith Rodin has indicated, the University of Pennsylvania is committed to cooperating with the appropriate federal agencies to address all questions concerning this research. Please contact me if you wish to discuss this point in greater detail.

Sincerely,

William N. Kelley, M.D.

Attention: Ann Ruffo Phelps

Attachments

c: Members of the Subcommittee Present
Honorable Jeff Bingaman
Honorable Christopher J. Dodd
Honorable Tim Hutchinson
Honorable James M. Jeffords
Honorable Edward M. Kennedy
Honorable Arlen Specter
Ruth Kirchstein, MD, Acting Director, National Institutes of Health
Jane E. Henney, Commissioner, U.S. Food and Drug Administration

ATTACHMENT A

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM
INSTITUTE FOR HUMAN GENE THERAPY
QUALITY ASSURANCE AND COMPLIANCE

Intramural Correspondence

3401 Market Street 215-573-5303
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MEMORANDUM

TO: James M. Wilson, M.D., Ph.D.
Joseph V. Hughes, Ph.D.
Lisa Speicher, Ph.D.
Nelson Wivel, M.D.
Steven Raper, M.D.
Mark Batshaw, M.D.

FROM: Philip J. Cross, M.S.

DATE: September 20, 1999

SUBJECT: Conversation with Dr. Amy Patterson, ORDA, 9/20/99

I telephoned Amy Patterson, Director, Office of Recombinant DNA Activities on September 20, 1999 to inform her of the fatality in the OTC clinical trial. This clinical trial was registered at ORDA as protocol #9512-139. I told her about the adverse events that were observed with this patient and she asked some general questions about the protocol. I told her that we would be filing a preliminary report today and then a follow-up report would be sent to her describing findings in more detail when they were available. I also mentioned that we would be willing to make a presentation concerning this patient at the next RAC meeting in December. She thanked me for our candor and our willingness to disseminate the information.

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

Institute for Human Gene Therapy

ATTACHMENT B

September 20, 1999

Amy Patterson, M.D.
Director
Office of Recombinant DNA Activities
National Institutes of Health
MSC 7010
6000 Executive Boulevard
Suite 302
Bethesda, MD 20892-7010

RE: Protocol #9512-139, Serious Adverse Event Report

Reference is made to protocol #9512-139 submitted by Mark Batshaw, M.D. for Ornithine Transcarbamylase Deficiency. Please accept, in duplicate, a Serious Adverse Event Report for patient #019 in this clinical study. This patient experienced several adverse events resulting in death. A preliminary report is attached. A follow-up report will be submitted when more information is obtained.

We are willing to present information concerning this patient at the next meeting of the Recombinant DNA Advisory Committee.

If you have any questions or comments please call me at (215) 573-5308.

Thank you for your attention to this matter.

Sincerely,

Philip J. Cross
Senior Associate Director
Quality Assurance and Compliance

Cc: James M. Wilson, M.D., Ph.D
Joseph V. Hughes, M.D.
Mark Batshaw, M.D.
Steven Raper, M.D.
Lisa Speicher, Ph.D.

SERIOUS ADVERSE EVENT
Institute for Human Gene Therapy
University of Pennsylvania Health System

ORDA Registration #9512-139

Protocol Title: Recombinant Adenovirus Gene Transfer in Adults with Partial Ornithine Transcarbamylase Deficiency (OTCD)

Patient Initials: JEGE
Patient Number: OTC.6624.019
Date of Birth: June 18, 1981
Gender: Male
Ethnicity: Caucasian

Date of Event: 9/17/99
Report Date: 9/20/99

Primary Adverse Event: Death

Description of Events:

JEGE, a 18-year-old male, with Partial Ornithine Transcarbamylase Deficiency was admitted to the Hospital of the University of Pennsylvania on Thursday, September 9, 1999 under Dr. Steve Raper as the attending physician for participation in the Phase I gene therapy trial mentioned above. JEGE was diagnosed with OTC (manifested as hyperammonemia) when he was 2.5 years of age. His physical exam on September 10, 1999 was unremarkable. On September 13, 1999 at midnight he began receiving IV alternative pathway therapy. On September 13 he received the OTC gene therapy infusion at a dose of 6×10^{11} particles per kg in the hepatic artery as per the protocol. The infusion began at 10:30 and ended at 12:30 p.m. The procedure went uneventfully. At approximately 2:00 p.m. he was transferred back to the GCRC and was placed in isolation as per the protocol. The first evening went as expected with back pain, fever, and nausea. The morning of September 14, 1999 he was noticed to be jaundiced. Hemolysis workup confirmed the diagnosis of sub-clinical DIC. He had several episodes of vomiting, was mildly hypotensive, febrile, tachycardic and he began to have mental status changes. Despite alternative pathway therapy, the patient experienced a rise in blood ammonia level. A CT scan without contrast of the brain was negative for internal bleeding or swelling. At approximately 3:00 p.m. he was transferred to the SICU for monitoring. The evening of September 14, 1999 he was prophylactically intubated and placed on hemodialysis for hyperammonemia not responsive to alternative pathway therapy. On September 15, he was pharmacologically paralyzed and sedated and continued to be mechanically ventilated. A rapidly progressive episode of ARDS developed which was unresponsive to standard ventilatory management. In the early morning hours of September 16, 1999 he was placed on extra corporeal membrane oxygenation (ECMO).

ECMO improved clinical parameters, however on 9/17 the patient became anuric and had elevation of transaminases to ALT 1500, AST 5000 confirming progressive renal and hepatic failure. NH4 remained at around 150. Progressive pressor doses were required to maintain pressure, as cardiac reserve was failing. Continuous veno-venous hemodialysis (CVVHD) was unable to remove excess volume. Neuro exam sowed no corneal reflexes, cold caloric stimulation, or oculocephalic reflex. Sonato-sensory evoked potentials

(SSEPs) were absent, and trans-cranial doppler (TCD) showed no flow. The recommendation to withdraw support was made to the family, who agreed. The patient was removed from ECMO and expired at 14:30 hrs. Permission for autopsy was granted, the M.E. released jurisdiction, and Kidney 1 declined to harvest organs.

Lawson, Becky (OD), 04:33 PM 9/21/99 , #9512-139/Serious Adverse Even

From: "Lawson, Becky (OD)" <LawsonB@odecsm2.od.nih.gov>
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Subject: #9512-139/Serious Adverse Event
Date: Tue, 21 Sep 1999 16:33:52 -0400
X-Mailer: Internet Mail Service (5.5.2650.10)

September 21, 1999

TO: Members, NIH Recombinant DNA Advisory Committee (RAC)

FROM: Debra Knorr, Executive Secretary, RAC

SUBJECT: Immediate Notification – Serious Adverse Event

This memorandum serves to notify the members of the RAC of a serious adverse event leading to the death of a patient on September 17, who was enrolled on NIH Human Gene Transfer Protocol # 9512-139: A Phase I Study of Adenoviral Vector Mediated Gene Transfer to Liver in Adults with Partial Ornithine Transcarbamylase Deficiency (OTC). The NIH Office of Recombinant DNA Activities (ORDA) is sending similar memoranda to the Chairs and Contacts of NIH-registered Institutional Biosafety Committees (IBCs), representatives of the Office for Protection from Research Risks (OPRR), and the Food and Drug Administration (FDA).

Mr. Philip Cross, Senior Associate Director of Quality Assurance and Compliance, Institute for Human Gene Therapy, University of Pennsylvania, immediately reported the details of this event to ORDA and FDA. The following information about this study and this serious adverse event is based on telephone communications with Mr. Cross and information currently on file with ORDA:

Patient: Male, 18 years of age

Vector Construct: H5.001CBhOTC -- an E1/E4-deleted, type 5 recombinant adenoviral vector, containing cytomegalovirus (CMV) enhanced chicken β-actin promoter expressing human ornithine transcarbamylase (OTC).

Route of Administration: Direct injection - intrahepatic artery

Dose: 6 x1011 particles per kilogram (highest proposed dose - second patient to receive this dose); total dose = 3.8 x 1013 particles

Date of Injection: September 13

Clinical Observations: Day 0 injection: fever, nausea, back pain
Day 1 post injection: hyperammonemia, jaundice
Days 2 to 4 post injection: disseminated intravascular coagulation, adult respiratory distress syndrome, and liver failure:
culminating in multi-system organ failure by Day 4

Date of Death: September 17 (4 days post injection)

Preliminary Cause of Death: Adult respiratory distress syndrome, multiple organ failure, and disseminated intravascular coagulation

Mr. Cross informed ORDA that an autopsy was conducted, and that comprehensive pathophysiological, histological, and molecular post-mortem analyses are being conducted to determine the exact cause of this event. Mr. Cross stated that the investigators intend to publish the results of these post-mortem studies as a case report, and they have agreed to present this case study to the RAC at its December 9-10, 1999, meeting.

ORDA commends the investigative team for reporting this event in a timely manner in compliance with the NIH reporting requirements set for in Appendix M-VII, of the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). In doing so, they have promoted continued accountability to the public by the human gene transfer research community. This accountability is essential for maintaining public trust and confidence in this novel field of medical research.

cc: Mark Batshaw, M.D., Principal Investigator, Children's National Medical Center, D.C.
James Wilson, M.D., Co-Investigator, University of Pennsylvania
Philip Cross, University of Pennsylvania
Gary Ellis, Ph.D., Office for Protection from Research Risks
Melody Lin, Ph.D., Office for Protection from Research Risks
Jeffrey Cohen, Ph.D., Office for Protection from Research Risks
Kathryn Zoon, Ph.D., Food and Drug Administration
Philip Noguchi, M.D., Food and Drug Administration
Lana Skirboll, Ph.D., National Institutes of Health
Amy Patterson, M.D., National Institutes of Health

Dr. FRIST. Thank you very much, the hearing is adjourned.
[Whereupon, at 12:55 p.m., the subcommittee was adjourned.]

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